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(71) Applicant *(for all designated States except US)*: KRENITSKY PHARMACEUTICALS INC. [US/US]; Four University Place, 4611 University Drive, Durham, NC 27707 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KELLEY, James, L. [US/US]; 10928 Raven Rock Drive, Raleigh, NC 27614 (US). KRENITSKY, Thomas, A. [US/US]; 106 Laurel Hill Road, Chapel Hill, NC 27514 (US). BEAUCHAMP, Lilia, M. [US/US]; 3003 Wycliff Road, Raleigh, NC 27607 (US).

(74) Agents: SPRUILL, W., Murray et al.; Bell Seltzer Intellectual Property Law Group, Alston & Bird LLP, P.O. Drawer 34009, Charlotte, NC 28234 (US).

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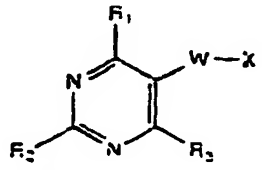
(57) Abstract



(I)

The present invention relates to novel derivatives of a series of substituted pyrimidines of formula (I); wherein W is O, CH2, CH2CH2, OCH2, CH2CH2CH2, or a bond; R^1 is hydroxyC1–6alkyloxyC1–6alkylamino, diC1–6alkylamino wherein the alkyl groups may be the same or different, aminoC1–6alkylamino, morpholino, piperidino, piperazino, piperazinoamino, homopiperazino, homopiperidino, homomorpholino, benzoxazino, indolino, 1,2,3,4–tetrahydroquinolino, benzylamino or anilino wherein C or N atoms may be substituted with one or more substituents; R^2 is selected from the group consisting of H; halogen; N3; OR; SR; C1–6alkyl; C6–10aryl; C6–10arylC1–6alkyl; C6–10heteroaryl; NR7R8; N=C(R11)N(R6)2; aziridino; azetidino; pyrrolidino; piperidino; hydroxypiperidino; heptamethyleneimino; piperazino; N–substituted piperazino homopiperazino; N–substituted homopiperazino; morpholino; homomorpholine; thiomorpholino; and R12C(O)C1–6alkyl; C–substituted piperidino; X is a C6–10aryl ring or a C6–10 heteroaryl ring optionally substituted with one or more suitable substituents for an aryl ring; R is H, C1–6alkyl, C3–8cycloalkyl, C6–10aryl or C6–10arylC1–6alkyl; provided that when –W–X is benzyl, R1 is not piperidine; and when R1 is a hydroxyalkyloxyalkylamino, R2 is not a heterocyclic ring; and to pharmaceutical compositions which contain them, to methods for their preparation and to their use in therapy, particularly in the treatment of neurodegenerative or other neurological disorders of the central and peripheral systems.

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SUBSTITUTED PYRIMIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEURODEGENERATIVE OR NEUROLOGICAL DISORDERS OF THE CENTRAL NERVOUS SYSTEM

BACKGROUND OF THE INVENTION

The present invention relates to novel derivatives of a series of substituted pyrimidines, to pharmaceutical compositions which contain them, to methods for their preparation and to their use in therapy, particularly in the treatment of neurodegenerative or other neurological disorders of the central and peripheral systems.

Dementing disorders such as age-related cognitive disorders, e.g., senility or Alzheimer's disease are medical conditions for which there are currently only limited therapies. Although studies suggest that multiple neurotransmitter systems are involved in senile dementia, a loss of cholinergic neurons and a severe depletion of choline acetyltransferase appear to show the earliest and strongest correlations with functional cognitive impairment [see P.T. Francis, A.M. Palmer, N.R. Sims, D.M. Bowen, A.N. Davison, M.M. Esiri, D. Neary, J.S. Snowden and G.K. Wilcock, Neurochemical Studies of Early-onset Alzheimer's Disease. N. Engl. J. Med., 313, 7 (1985); R.T. Bartus, R.L. Dean, M. Pontecorvo and C. Flicker, The Cholinergic Hypothesis: A Historical Overview, Current Perspective, and Future Directions. Ann. N. Y. Acad. Sci., 444, 332 (1985); F. Hefti and L.S. Schneider, Nerve Growth Factor and Alzheimer's Disease, Clin. Neuropharmacol., 14, S62 (1991)]. Several groups have attempted to stimulate cholinergic activity by blocking the breakdown of acetylcholine with acetylcholine esterase inhibitors or by introducing muscarinic or nicotinic agonists [see R.T. Bartus, R.L. Dean III, B. Beer and A.S. Lippa, The Cholinergic Hypothesis of Geriatric Memory Dysfunction. Science, 217, 408 (1982); J. Varghese, I. Lieberburg and E.D. Thorsett, Chapter 21. Alzheimer's Disease: Current Therapeutic Approaches. Annu. Rep. Med. Chem., 28, 197 (1993)]. The approved drugs Cognex® and Aricept® are acetylcholine esterase inhibitors.

Nerve growth factor (NGF) is the best characterized neurotropic factor that is capable of inducing cell differentiation of neural cells and promoting neurite

sprouting. The neurotrophic protein NGF primarily affects cholinergic neurons in the central nervous system and may be necessary for their survival [see F. Hefti and P.A. Lapchak, Pharmacology of Nerve Growth Factor in the Brain. Adv. Pharmacol., 24, 239 (1993)]. NGF is not systemically bioavailable, but if it is injected or infused directly into brain, it prevents neuronal cell loss and restores cognitive function in aged or lesioned rats or monkeys [see W. Fischer, A. Bjorklund, K. Chen and F.H. Gage, NGF Improves Spatial Memory in Aged Rodents as a Function of Age. J. Neurosci.,11, 1889 (1991)]. NGF effects ultimately result in the stimulation of choline acetyltransferase, the enzyme for biosynthesis of acetylcholine and the promotion of neurite growth. Consequently, small molecules that produce neurotrophic or "nerve growth factor-like" (NGF-like) properties in mammalian cell cultures have potential for use in the treatment of dementing disorders such as age-related senility or Alzheimer's disease and other neurodegenerative conditions such as peripheral neuropathies, Parkinson's, stroke damage, transient ischemic attacks or trauma-head injuries.

There are several reports of small molecules that exhibit various aspects of NGF-like activity. Isaxonine [2-(isopropylamino)pyrimidine] was developed as a neurotrophic pharmaceutical but the clinical application was withdrawn, possibly due to toxicological effects [see Neuropathies peripheriques et a l'isaxonine. Nouv. Presse Med., 11, 1189 (1982); S. Lehmann, C. Quirosa-Guillou, U. Becherer, C. Thal and J.-P. Zanetta, Neurite Outgrowth of Neurons of Rat Dorsal Root Ganglia Induced by New Neurotrophic Substances with Guanidine Group. Neurosci. Lett., 152, 57 (1993)]. Several 2-(piperazino)pyrimidine derivatives were reported to possess NGF-like activity and are being studied further for use in treating CNS degenerative diseases [see A.
Awaya, H. Kobayashi, K. Horikomi, S. Tanaka, A.M. Kabir, K. Yokoyama,H. Ohna, K. Kato, T. Kitahara, I. Tomino, S. Isayama and S. Nakamura, Neurotrophic Pyrimidine Heterocyclic Compounds. I. The Newly Synthesized Pyrimidine Compounds Promote Neurite Outgrowth of GOTO and Neuro 2a Neuroblastoma Cell Lines, and Potentiate Nerve Growth Factor (NGF)-Induced Neurite Sprouting of PC-12 Cells. Biol. Pharm. Bull., 16, 248 (1993)]. AIT-082 (4[[3-(1,6-dihydro-6-oxo-9-purin-9-yl)-1-oxopropyl]amino]benzoic acid) is reported to enhance NGF action in cultured PC-12

cells and to restore age-induced working memory deficits in mice [see P.J.. Middlemiss, A.J. Glasky, M.P. Rathbone, E. Werstuik, S. Hindley and J. Gysbers, AIT-082, A Unique Purine Derivative, Enhances Nerve Growth Factor Mediated Neurite Outgrowth from PC-12 cells. Neuroscience Let., 199, 131 (1995)]. In addition, U.S. Patent 5,075,305 discloses 2-amino-5-bromo-4-(morpholino)pyrimidine as having NGF-like properties and its possible use in treating CNS degenerative diseases like Alzheimer's disease as well as peripheral neuropathies or other peripheral nervous system disorders.

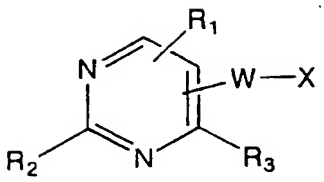
SUMMARY OF THE INVENTION

We have now discovered a series of substituted pyrimidines that demonstrate NGF-like activity and/or enhancement of NGF activity in PC12 cells. The compounds stimulated both neurite outgrowth and choline acetyltransferase activity in *in vitro* experiments. Such activities are predictive for causing increased choline acetyltransferase activity in rat striatum and improving cognitative performance in animal models of age-induced working memory deficits by potentiating the activity of endogenous NGF in the brain. [see P.J.. Middlemiss, A.J. Glasky, M.P. Rathbone, E. Werstuik, S. Hindley and J. Gysbers, AIT-082, A Unique Purine Derivative, Enhances Nerve Growth Factor Mediated Neurite Outgrowth from PC-12 cells. Neuroscience Let., 199, 131 (1995); A.J. Glasky, C.L. Melchior, B. Pirzadeh, N. Heydari and R.F. Ritzmannn, Effect of AIT-082, a Purine Analog, on Working Memory in Normal and Aged Mice. Pharmacol. Biochem. Behav., 47, 325 (1994); R. Morris, Developments of a Water-maze Procedure for Studying Spatial Learning in the Rat. J. Neurosci. Methods, 11, 47 (1984)].

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, there are provided novel compounds of Formula I:

Formula I



wherein

W is O, CH2, CH2CH2, OCH2, CH2CH2CH2, or a bond;

R^1 is hydroxyC1-6alkyloxyC1-6alkylamino, diC1-6alkylamino (wherein the alkyl groups may be the same or different); or aminoC1-6alkylamino, morpholino, piperidino, piperazino, piperazinoamino, homopiperazino, homopiperidino, homomorpholino, benzoxazino, indolino, 1,2,3,4-tetrahydroquinolino, benzylamino, anilino wherein C or N atoms may be substituted with one or more substituents selected from the group consisting of:

NR4R5 (wherein R4 and R5 may be the same or different and are H, C1-6alkyl,

hydroxyC1-6alkyl, C3-8cycloalkyl, C6-10aryl, C6-10arylC1-6alkyl, C1-6alkoxy,

C6-10aryloxy or C6-10arylC1-6alkoxy);

NR4R5carbonyC1-6alkyl (wherein R4 and R5 may be the same or different);

OH;

CN;

C1-6alkyl;

C2-7alkenyl;

C2-7alkynyl;

C6-10aryl;

C6-10heteroaryl;

hydroxyC1-6alkyl;

dihydroxyC1-6akyl;

C1-6alkoxy;

C1-6aryloxy;

C6-10heteroaryloxy;

hydroxyC1-6alkoxy;

C1-6alkoxyC1-6alkyl;
C6-10aryloxyC1-6alkyl;
C6-10heteroaryloxyC1-6alkyl;
C3-8cycloalkyl;
C6-10arylC1-6alkyl;
C6-10heteroarylC1-6alkyl;
C6-10arylC1-6alkoxy;
C6-10heteroarylC1-6alkoxy;
C1-6alkylcarbonylC1-6alkyl;
C6-10arylcarbonylC1-6alkyl;
carboxyC1-6alkyl;
C1-6alkoxycarbonylC1-6alkyl;
C6-10aryloxycarbonylC1-6alkyl;
C6-10arylC1-6alkyloxycarbonylC1-6alkyl;
cyanoC1-6alkyl
C1-6alkylthioC1-6alkyl;
C1-6alkylsulfinylC1-6alkyl;
C1-6alkylsulfonylC1-6alkyl;
C6-10arylthioC1-6alkyl;
C6-10arylsulfinylC1-6alkyl;
C6-10arylsulfonylC1-6alkyl;
C6-10arylC1-6alkylthioC1-6alkyl;
C6-10arylC1-6alkylsulfinylC1-6alkyl;
C6-10arylC1-6alkylsulfonylC1-6alkyl;
C6-10heteroarylthioC1-6alkyl;
C6-10heteroarylsulfinylC1-6alkyl;
C6-10heteroarylsulfonylC1-6alkyl;
aziridino;
azetidino;
pyrrolidino;
piperidino;
heptamethyleneimino;
homopiperazino;

N-substituted homopiperazino (wherein the substituent may be C1-6alkyl, C6-10aryl, C6-10arylC1-6alkyl or C6-10heteroaryl);

piperazino;

N-substituted piperazino (wherein the substituent may be C1-6alkyl, C6-10aryl, C6-10 arylC1-6alkyl or C6-10heteroaryl);

morpholino;

homomorpholine;

thiomorpholino;

aminoC1-6alkyl;

C1-6alkylaminoC1-6alkyl;

di(C1-6alkyl)aminoC1-6alkyl (wherein the alkyl groups may be the same or different);

C6-10arylaminoC1-6alkyl;

C6-10arylC1-6alkylaminoC1-6alkyl;

di(C6-10aryl)aminoC1-6alkyl (wherein the aryl groups may be the same or different);

di(C6-10arylC1-6alkyl)aminoC1-6alkyl (wherein the arylalkyl groups may be the same or different);

R12C(O)C1-6alkyl (wherein R12 is aziridino, azetidino, pyrrolidino, piperidino, heptamethyleneimino, piperazino, homopiperazino, morpholino, homomorpholino, or thiomorpholino);

C(O)R6; C(O)C(O)R6; C(S)R6; S(O)2R6; and C(NR11)R6 (wherein R11 is hydrogen, C1-6alkyl or C6-10aryl and R6 may be H or any of the above listed substituents); and

R^2 is selected from the group consisting of:

H;

halogen;

N3;
OR;
SR;
C1-6alkyl;
C6-10aryl;
C6-10arylC1-6alkyl;
C6-10heteroaryl;
NR7R8 (wherein R7 and R8 may be the same or different and are H, C1-6alkyl, hydroxyC1-6alkyl, hydroxyC1-6alkyloxyC1-6alkyl; C3-8cycloalkyl, C6-10aryl, C6-10arylC1-6alkyl, C1-6alkoxy, C6-10aryloxy, C6-10arylC1-6alkoxy, C(O)R6, C(O)C(O)R6, C(S)R6, S(O)2R6, or C(NR11)R6);
N=C(R11)N(R6)2;
aziridino;
azetidino;
pyrrolidino;
piperidino;
hydroxypiperidino;
heptamethyleneimino;
piperazino;
N-substitued piperazino (wherein the substituent may be C1-6alkyl, hydroxyC1-6alkyl, C6-10aryl, C6-10arylC1-6alkyl or C6-10heteroaryl);
homopiperazino;
N-substituted homopiperazino (wherein the substituent may be C1-6alkyl, hydroxyC1-6alkyl, C6-10aryl, C6-10arylC1-6alkyl or C6-10heteroaryl);
morpholino;
homomorpholine;
thiomorpholino; and
R12C(O)C1-6alkyl (wherein R12 is aziridino, azetidino, pyrrolidino, piperidino, heptamethyleneimino, piperizino, homopiperazino, morpholino,

homomorpholino, or thiomorpholino);

C-substituted piperidino wherein the substituent is C(O)R6);

C-substituted piperidino (wherein the substituent may be C1-6alkyl, hydroxyC1-6alkyl, C6-10aryl, C6-10arylC1-6alkyl or C6-10heteroaryl);

R^3 is selected from the group consisting of:

H;

OR;

NR9R10 (wherein R9 and R10 may be the same or different and are H, C1-6alkyl,

C3-8cycloalkyl, C6-10aryl, or C6-10arylC1-6alkyl);

CF3;

C1-6alkyl;

C6-10aryl;

C6-10arylC1-6alkyl; and

C6-10heteroaryl;

X is a C6-10 aryl ring or a C6-10 heteroaryl ring optionally substituted with one or more suitable substituents for an aryl ring, preferably selected from the group consisting of:

halogen;

C1-6 alkyl;

C2-7alkenyl;

C2-7alkynyl;

C6-10aryl;

C6-10heteroaryl;

OR;

NR9R10 (wherein R9 and R10 may be the same or different and are H, C1-6alkyl,

C3-8cycloalkyl, C6-10aryl, or C6-10arylC1-6alkyl);

NROR;

C(O)NR9R10

C(O)OR;
C(O)R;
NRC(O)NR9R10
NRC(O)R;
NRC(O)OR;
CR(OH)R;
OC(O)R;
S(O)nR wherein R is other than H and n is 0, 1 or 2;
NRS(O)mR wherein R is other than H and m is 1 or 2;
S(O)2NR9R10;
NO2;
CN; and
CF3;
OCF3;

R is H, C1-6alkyl, C3-8cycloalkyl, C6-10aryl or C6-10arylC1-6alkyl; provided that when -W-X is benzyl, R1 is not piperidine; and when R1 is a hydroxyalkyloxyalkylamino, R2 is not a heterocyclic ring;

and pharmaceutically acceptable esters, amides, salts or solvates thereof.

The present invention includes all enantiomeric and diastereomeric forms of the compounds of Formula I either individually or admixed in any proportion.

The compounds of Formula I above and their pharmaceutically acceptable salts or solvates are sometimes hereinafter referred to as "the compounds according to the invention".

By "alkyl" is meant straight or branched chain alkyl. The alkyl groups may be optionally substituted with hydroxy, amino or halogen.

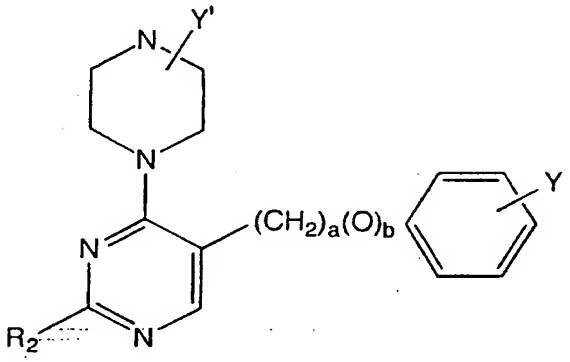
By "aryl" is meant an aromatic ring such as phenyl or naphthyl;

By "heteroaryl" is meant a ring containing 1 to 4 heteroatoms selected from the group consisting of N, O and S.

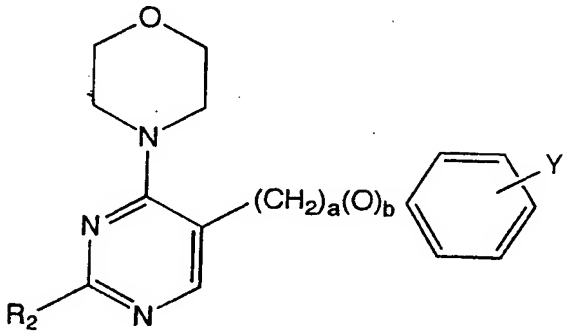
By "halogen" is meant F, Cl, Br or I.

Preferred compounds included in the present invention are more particularly defined by the following Formulas IA - ID:

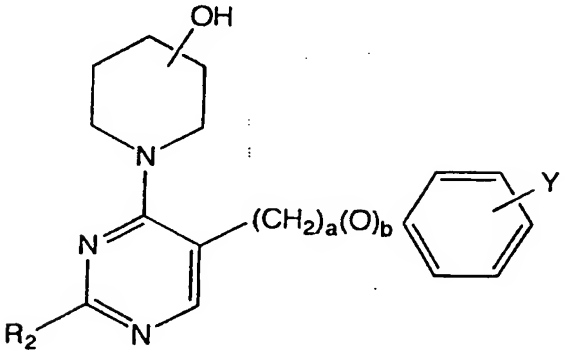
Formula IA



Formula IB



Formula IC



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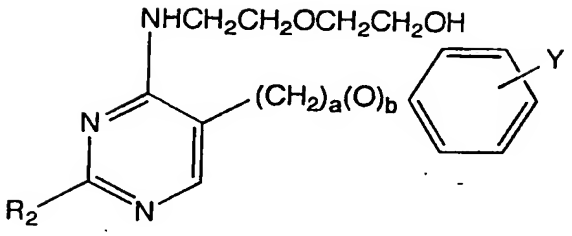
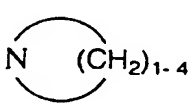
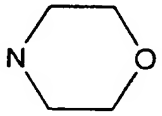
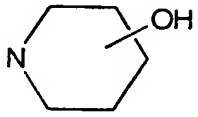


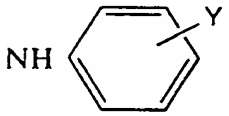
wherein a and b are 0 or 1 and a+b = 0 or 1 and most preferably a+b =1;

R2 is selected from the group consisting of : NH2, NHC1-6alkyl, NHC2H4OC2H4OC2H4OH,

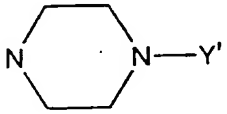








and



provided that in Formula ID, R2 is not a heterocyclic;

Y is any suitable substituent for an aryl ring, and Y' is selected from the group consisting of:
H, CH3, CH2CH3, CH2CH2OH, C(O)R, S(O)2R and C6H5,

and pharmaceutically acceptable esters, amides, salts or solvates thereof.

Particularly preferred compounds of Formula I are those wherein R1 is attached to the 4-position of the pyrimidine ring, W is O, CH2 or CH2CH2 and X is substituted phenyl; and pharmaceutically acceptable salts or solvates thereof.

More preferred compounds of Formula I are those wherein R1 is attached to the 4-position of the pyrimidine ring, W is O or CH2 and X is substituted phenyl; and pharmaceutically acceptable salts or solvates thereof.

Most preferred compounds of Formula I are those wherein R1 is attached to the 4-position of the pyrimidine ring and is 4-(2-hydroxyethyl)piperazino or 2-(2-hydroxyethoxy)ethylamino, W is O or CH2, X is substituted phenyl, and R2 is NH2; and pharmaceutically acceptable salts or solvates thereof.

Specifically preferred compounds of Formula I are:

2-Amino-4-morpholino-5-(phenoxy)pyrimidine
2-Amino-5-(4-methylphenoxy)-4-(morpholino)pyrimidine
2-Amino-5-(4-fluorophenoxy)-4-(morpholino)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine
2-Amino-5-(4-chlorobenzyloxy)-4-(morpholino)pyrimidine
2-Amino-5-(benzyloxy)-4-(morpholino)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(2-(2-hydroxyethoxy)ethylamino)pyrimidine
2-Amino-4-(4-carbamoylpiperidino)-5-(4-chlorophenoxy)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(piperazino)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(4-methylpiperazino)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(4-ethylpiperazino)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine
2-Amino-5-(4-fluorophenoxy)-4-(4-phenylpiperazino)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(4-phenylpiperazino)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(4-(2-pyridyl)piperazino)pyrimidine
2-Amino-4-(4-benzylpiperazino)-5-(4-chlorophenoxy)pyrimidine
2-Amino-5-(4-chlorophenyoxy)-4-(4-formylpiperazino)pyrimidine
4-(4-Acetylpiperazino)-2-amino-5-(4-chlorophenoxy)pyrimidine
2-Amino-5-(4-chlorophenoxy)-4-(4-methoxyacetylpiperazino)pyrimidine
2-Anilino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine
5-(4-Chlorophenoxy)-2-(dimethylamino)-4-(4-methylpiperazino)pyrimidine
5-(4-Chlorophenoxy)-4-morpholino-2-(3-phenylureido)pyrimidine

5-(4-Chlorophenoxy)-2,4-(dimorpholino)pyrimidine

5-(4-Chlorophenoxy)-2-(4-methylpiperazino)-4-(morpholino)pyrimidine

5-(4-Chlorophenoxy)-4-(4-methylpiperazino)-2-(morpholino)pyrimidine

5-(4-Chlorophenoxy)-4-[4-(2-hydroxyethyl)piperazino]-2-(morpholino)pyrimidine

2-Amino-5-benzyl-4-(morpholino)pyrimidine

2-Amino-5-benzyl-4-(dimethylamino)pyrimidine

2-Amino-5-(4-methoxybenzyl)-4-(morpholino)pyrimidine

5-Benzyl-4-[2-(2-hydroxyethoxy)ethylamino]pyrimidine

2-Amino-5-benzyl-4-(4-hydroxypiperidino)pyrimidine

2-Amino-5-benzyl-4-(4-methylpiperazinoamino)pyrimidine

2-Amino-5-benzyl-4-(4-carbamoylpiperidino)pyrimidine

2-Amino-5-benzyl-4-(4-methylpiperazino)pyrimidine

2-Amino-5-benzyl-4-(4-hydroxyethylpiperazino)pyrimidine

5-Benzyl-2,4-bis(4-methylpiperazino)pyrimidine

5-Benzyl-2,4-(dimorpholino)pyrimidine

5-Benzyl-2-dimethylamino-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine

2-Amino-4-(4-ethylpiperazino)-5-(4-methylbenzyl)pyrimidine

2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-methylbenzyl)pyrimidine

2-Amino-4-(4-hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine

2-Amino-5-(4-chlorobenzy)-4-(morpholino)pyrimidine

2-Amino-4-[2-(2-hydroxyethyl)ethylamino]-5-(4-chlorobenzyl)pyrimidine

2-Amino-5-(4-chlorobenzyl)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-chlorobenzyl)-4-(4-ethylpiperazino)pyrimidine

2-Amino-5-(4-chlorobenzyl)-4-(4-hydroxyethylpiperazino)pyrimidine

2-Amino-5-(4-chlorobenzyl)-4-(4-hydroxypiperidino)pyrimidine

2-Amino-5-(4-methoxybenzyl)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-hydroxybenzyl)-4-(4-methylpiperazino)pyrimidine

2-Amino-4-(4-methylpiperazino)-5-(4-isopropylbenzyl)pyrimidine

2-Amino-4-(4-ethylpiperazino)-5-(4-isopropylbenzyl)pyrimidine

2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-isopropylbenzyl)pyrimidine

2-Amino-5-(4-hydroxypiperidino)-5-(4-isopropylbenzyl)pyrimidine

2-Amino-4-(4-methylpiperazino)-5-(3,4,5-trimethoxybenzyl)pyrimidine
2-Amino-4-(4-ethylpiperazino)-5-(3,4,5-trimethoxybenzyl)pyrimidine
2-Amino-4-(4-hydroxyethylpiperazino)-5-(3,4,5-trimethoxybenzyl)pyrimidine
2-Amino-4-(4-hydroxypiperidino)-5-(3,4,5-trimethoxybenzyl)pyrimidine
2-Amino-4-(4-methylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)pyrimidine
2-Amino-4-(4-ethylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)pyrimidine
2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)pyrimidine
2-Amino-4-(4-methylpiperazino)-5-((3-pyridyl)methyl)pyrimidine
2-Amino-4-(4-ethylpiperazino)-5-[(3-pyridyl)methyl]pyrimidine
2-Amino-4-(4-hydroxyethylpiperazino)-5-([3-pyridyl]methyl)pyrimidine
4-Anilino-2-methyl-5-(phenethyl)pyrimidine
4-Benzylamino-2-methyl-5-(phenethyl)pyrimidine
4-[2-(2-Hydroxyethoxy)ethylamino]-2-methyl-5-(phenethyl)pyrimidine
2-Methyl-4-morpholino-5-(phenethyl)pyrimidine
2,4-Dimorpholino-5-(phenethyl)pyrimidine
2-Amino-4-morpholino-5-(phenethyl)pyrimidine
4-Morpholino-5-(phenethyl)pyrimidine
2-Amino-5-(4-methoxyphenethyl)-4-(morpholino)pyrimidine
2-Amino-4-morpholino-5-(phenylpropyl)pyrimidine
2-Amino-4-morpholino-5-(phenyl)pyrimidine
2-Amino-5-(4-fluorophenyl)-4-(morpholino)pyrimidine
2-Amino-5-(4-chlorophenyl)-4-(morpholino)pyrimidine
2-Amino-5-(4-bromophenyl)-4-(morpholino)pyrimidine
2-Amino-4-(4-chlorophenoxy)-5-(morpholino)pyrimidine
2-Amino-4-(4-chlorobenzyloxy)-5-(4-methylpiperizino)
2-Amino-4-(4-chlorophenoxy)-5-(4-methylpiperizino)pyrimidine
4-(4-Chlorophenoxy)-5-(4-methylpiperazino)pyrimidine
2-Amino-4-(chlorobenzylamino)-5-(4-methylpiperazino);
2-Amino-5-(4-ethylphenoxy)-4-(4-methylpiperazino)pyrimidine
2-Amino-5-(2,4-dichlorophenoxy)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-chloro-2-methylphenoxy)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(3-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(2-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(4-bromophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(4-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(3-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-trifluoromethylphenoxy)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-methylphenoxy)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(3-methylphenoxy)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino-5-(2-methylphenoxy))pyrimidine

2-Amino-5-(4-ethylphenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-isopropylphenoxy)pyrimidine

2-Amino-5-(4-butylphenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-methoxyphenoxy)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(3-methoxyphenoxy)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(2-methoxyphenoxy)pyrimidine

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-(trifluoromethoxy)phenoxy)pyrimidine

2-Amino-5-(2,4-dichlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(2,3-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(2,4-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(2,6-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(3,5-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(4-chloro-2-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(2-chloro-4-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(4-chloro-2-methylphenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-(2-pivaloyloxyethyl)piperazino)pyrimidine

2-Amino-4-(4-butyrylpiperazino)-5-(4-chlorophenoxy)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-phenoxyacetylpiperazino)pyrimidine

2-Amino-4-(4-benzoylpiperazino)-5-(4-chlorophenoxy)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-(2-furoyl)piperazino)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-ethoxycarbonylpiperazino)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-phenoxycarbonylpiperazino)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-methoxydicarbonylpiperazino)pyrimidine

2-Amino-4-(4-(3-carbamoylpropionyl)piperazino)-5-(4-chlorophenoxy)pyrimidine

2-Amino-4-(4-(3-carboxypropionyl)piperazino)-5-(4-chlorophenoxy)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-(methlysulfonyl)piperazino)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-(phenylsulfonyl)piperazino)pyrimidine

5-(4-Chlorophenoxy)-4-(4-methylpiperazino)-2-(1-pyrrolidinyl)pyrimidine

2-(Anilino)-5-(4-chlorophenoxy)-4-(4-methylpiperazino)pyrimidine

5-(4-Chlorophenoxy)-2-(4-fluoroanilino)-4-(4-methylpiperazino)pyrimidine

2-(Benzylamine)-5-(4-chlorophenoxy)-4-(4-methylpiperazino) pyrimidine

2,4-Bis(4-ethylpiperazino)-5-(4-chlorophenoxy)pyrimidine

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(isopropylamino) pyrimidine

5-(4-Chlorophenoxy)-2-((2-hydroxyethyl)amino)-4-(4-(2-hydroxyethyl)piperazino) pyrimidine

5-(4-Chlorophenoxy)-2-(2-(2-hydroxyethoxy)ethylamino)-4-(4-(2-hydroxyethyl)piperazino) pyrimidine

2-(Anilino)-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

5-(4-Chlorophenoxy)-2-(4-fluoroanilino)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(4-methylanilino)pyrimidine

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(1-pyrrolidinyl)pyrimidine

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(piperidino)pyrimidine

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(4-hydroxypiperidino) pyrimidine

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(4-phenylpiperazino) pyrimidine

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(4-methylpiperazino) pyrimidine

5-(4-Chlorophenoxy)-2-(4-ethylpiperazino)-4-(4-(2-hydroxyethyl)piperazino) pyrimidine

2,4-Bis(4-(2-hydroxyethyl)piperazino)-5-(4-chlorophenoxy)pyrimidine

2-Chloro-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

5-(4-Chlorophenoxy)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-chlorophenyl)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(4-chlorophenyl)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-fluorobenzyl)-4-(4-methylpiperazino)pyrimidine

2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-trifluoromethylbenzyl)pyrimidine

2-(4-Carbamoylpiperidino)-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine

2-(2-Hydroxyethoxy)ethylamino)-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-chlorophenethyl)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-chlorophenethyl)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(4-chlorobenzyloxy)-4-(4-methylpiperazino)pyrimidine

2-Amino-5-(4-chlorobenzyloxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(4-hydroxypiperidino)pyrimidine

2-Amino-4-(4-hydroxypiperidino)-5-(4-methylphenoxy)pyrimidine

2-Amino-5-(2,4-dichlorophenoxy)-4-(4-hydroxypiperidino)pyrimidine

5-(4-Chlorophenoxy)-4-(4-hydroxypiperidino)-2-morpholinopyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(3-(hydroxymethyl)piperidino)pyrimidine

2-Amino-5-(4-chlorophenoxy)-4-(2-(2-hydroxyethyl)piperidino)pyrimidine

5-(4-Chlorophenoxy)-4-(2-(2-hydroxyethoxy)ethylamino)-2-morpholinopyrimidine

2-Anilino-4-(4-hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine

2,4-Bis-(4-Hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine

4-(4-Hydroxypiperidino)-5-(phenethyl)pyrimidine

2-Amino-4-(4-carbamoylpiperidino)-5-(4-chlorophenethyl)pyrimidine

and pharmaceutically acceptable salts or solvates thereof.

In one aspect of the invention there is provided the compounds according to the invention for use in medical therapy particularly for the treatment of neurodegenerative or neurological disorders of the central or peripheral nervous systems.

Examples of nervous system disorders which may be treated in accordance with the invention include dementing disorders such as age-related senility, senile dementia or Age Related Mental Impairment (ARMI), cerebal ataxia, Parkinson's disease, Alzheimer's disease, peripheral neuropathy, cognitive disorders secondary to stroke or trauma and attention-deficit hyperactivity disorder.

In a further aspect of the present invention there is included:

a) A method for the treatment of neurodegenerative or neurological disorders of the central or peripheral nervous systems which comprises treating the subject e.g., a mammal, such as a human, with a therapeutically effective amount of a compound according to the invention.

b) Use of a compound according to the invention in the manufacture of a medicament for the treatment of any of the above-mentioned disorders.

Examples of pharmaceutically acceptable salts of the compounds according to the invention include acid addition salts. However, salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question.

Preferred salts include those formed from hydrochloric, hydrobromic, sulfuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, oxaloacetic, methanesulfonic, ethansulfonic, p-toluenesulfonic, benzenesulfonic and isethionic acids.

The compounds according to the invention and pharmaceutically acceptable salts or solvates thereof may be employed in combination with other therapeutic agents for the treatment of the above disorders. Examples of such further therapeutic agents include Cognex®, Aricept® and other agents (e.g., acetylcholine esterase inhibitors, muscarinic or nicotinic receptor agonists, MAO inhibitors) that are effective for the treatment of neurodegenerative or neurological disorders of the central or peripheral nervous systems. The component compounds of such combination therapy may be administered simultaneously in either separate or combined formulations, or at different times, e.g., sequentially such that a combined effect is achieved.

While it is possible for compounds according to the invention to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. The formulations of the present invention comprise a compound of Formula I, as above defined, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, transdermal, intradermal, intramuscular and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon, for example, the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be

prepared by any of the methods well know in the art of pharmacy. All methods include the step of bringing into association a compound of Formula I or a pharmaceutically acceptable salt thereof (active ingredient) with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion, or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacterioistats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophillised) condition requiring only the addition of the sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous

injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport or iontophoresis, as generally described in Pharmaceutical. Res., **3**(6), 318 (1986).

Formulations for rectal administration may be presented as suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example, buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Tablets or other forms of presentation in discrete units may conveniently contain an amount of compound of the Formula I which is effective for each of the above-mentioned indications at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually between 10 mg to 250 mg.

For the above-mentioned conditions and disorders, the compounds of the Formula I are preferably administered orally or by injection (intraparenteral or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also the route of administration is likely to vary depending on the condition and its severity.

For each of the above-mentioned indications the compounds of the Formula I may be administered orally. The dose range for adult humans is generally from about 10 to 4000 mg/day and preferably from about 100 to 1000 mg/day. It may be advantageous to administer an initial dose of 200 to 2000 mg the first day then a lower dose of 100 to 1000 mg on subsequent days.

For each of the above-mentioned indications, the compounds according to the invention may be administered by injection at a dose of from 30 to 800 mg/kg per day.

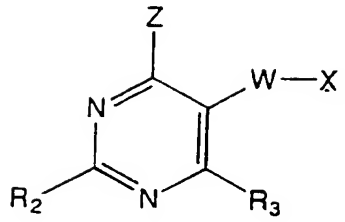
The present invention further includes processes for the preparation of compounds of Formula I and salts or solvates thereof.

The compounds of formula (I) and their esters, amides, salts and solvates may be prepared in any manner known in the art for the preparation of compounds of analogous structure, for example, in accordance with the present invention, by those methods hereinafter described.

The compounds, esters, amides, salts and solvates of formula (I) wherein R1 is attached to the 4-position of the pyrimidine ring and W-X is attached at the 5-position of the pyrimidine ring may thus be prepared by a process which comprises:

reacting a compound of formula (IIA)

Formula IIA

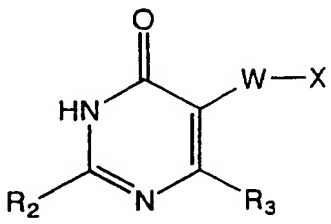


wherein R2, R3, W and X are as hereinbefore defined and Z is a leaving group, with an amine NR'R" (wherein R' and R" are as defined for R^1) or a suitable derivative thereof. Suitable leaving groups include halogens such as chlorine. The reaction is carried out in an organic solvent (e.g., ethanol, N,N-dimethylformamide) at a temperature of approximately 20°C to approximately 100°C. The compound of formula (IIA) may be isolated and purified prior to reaction with an amine NR'R" or may be used *in situ*.

Compounds of formula (IIA), wherein R^2, R^3, W and X are as hereinbefore defined and Z is a 1-(4-formylpiperazino), 1-(4-substituted cabonylpiperazino) or 1-(4-substituted sulfonylpiperazino) derivative, can be prepared from compounds of formula (IIA), wherein R^2, R^3, W and X are as hereinbefore defined and Z is 1-(piperazino), by reaction with a carbonylating agent (e.g., ethyl formate, acetic anhydride, methoxyacetyl chloride, benzoyl chloride, methyl isocyanate, ethyl chloroformate, methanesulfonyl chloride) and a suitable base (e.g., 4-dimethylaminopyridine, pyridine, triethylamine, potassium carbonate) in a suitable organic solvent (e.g., tetrahydrofuran, acetone, methanol, pyridine, N,N-dimethylformamide) at a temperature of 0°C to 60°C.

Compounds of formula (IIA) wherein Z is a halogen atom can be prepared from compounds of formula (IIIA)

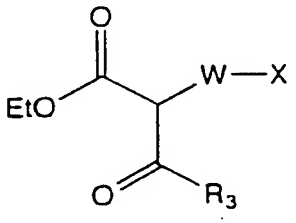
Formula IIIA



wherein R^2, R^3, W and X are as hereinbefore defined by reaction with a halogenating agent (e.g., Vilsmeier reagent (e.g., oxalyl chloride and N,N-dimethylformamide, oxalyl chloride and 1-formylmorpholine, oxalyl chloride and N,N-diisopropylformamide), phosphorous oxychloride, phosphorous pentachloride, thionyl chloride) in a suitable organic solvent (e.g., dichloromethane, 1,2-dichlorethane, toluene, N,N-dimethlyformamide) at a temperature of approximately 40°C to approximately 100°C.

Compounds of formula (IIIA) can be prepared from compounds of formula (IVA)

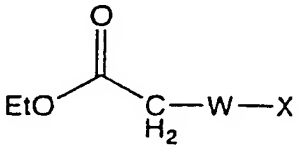
Formula IVA



wherein R^3, W and X are as hereinbefore defined by reaction of an alkaline earth salt of (IVA) with formamidine or a derivative of formamidine (e.g., guanidine, N,N-dialkylguanidine, N-phenylguanidine, thiourea, 2-ethyl-2-thiopseudourea, acetamidine) in a suitable organic solvent (e.g., ethanol, methanol, 2-propanol, tert-butanol, tetrahydrofuran) at a temperature of approximately 60°C to the reflux temperature.

Compounds of formula (IVA) can be prepared from compounds of formula (VA)

Formula VA



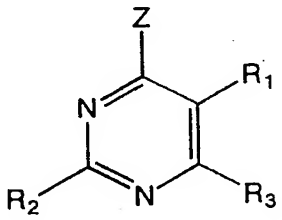
where in W and X are as hereinbefore defined by reaction with an ester (e.g., ethyl formate, ethyl acetate, ethyl benzoate, ethyl trifluoroacetate) and a strong base (e.g., sodium hydride, potassium hydride, potassium tert-butoxide, sodium metal, lithium diisopropylamine) in a suitable organic solvent (e.g., tetrahydrofuran, ether, toluene) at a temperature of approximately 0°C to approximately 40°C.

Compounds of formula (VA) can be prepared by various methods known in the art or are available from commercial sources.

The compounds, esters, amides, salts and solvates of formula (I) wherein R1 is attached to the 5-position of the pyrimidine ring and W-X is attached to the 4-position of the pyrimidine ring may thus be prepared by a process which comprises:

reacting a compound of formula (IIB)

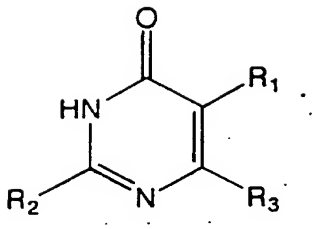
Formula IIB



wherein R^1, R^2 and R^3 are as hereinbefore defined and Z is a leaving group, with an amine NHCH2X or NHRX (wherein R and X are as defined hereinbefore) or an alcohol HOX or HOCH2X or a suitable derivative thereof. Suitable leaving groups include halogens such as chlorine. The reaction is carried out with a suitable base (e.g., 4-dimethylaminopyridine, pyridine, triethylamine, potassium carbonate, sodium hydride, potassium t-butoxide) in a suitable organic solvent (e.g., tetrahydrofuran, acetone, methanol, pyridine, N,N-dimethylformamide) at a temperature of approximately 20°C to approximately 100°C. The compound of formula (IIA) may be isolated and purified prior to reaction with an amine NR'R" or may be used *in situ*.

Compounds of formula (IIB) wherein Z is a halogen atom can be prepared from compounds of formula (IIIB)

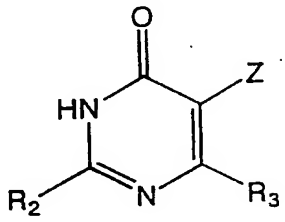
Formula IIIB



wherein R^1, R^2 and R^3 are as hereinbefore defined by reaction with a halogenating agent (e.g., Vilsmeier reagent (e.g., oxalyl chloride and N,N-dimethylformamide, oxalyl chloride and 1-formylmorpholine, oxalyl chloride and N,N-diisopropylformamide), phosphorous oxychloride, phosphorous pentachloride, thionyl chloride) in a suitable organic solvent (e.g., dichloromethane, 1,2-dichlorethane, toluene, N,N-dimethlyformamide) at a temperature of approximately 40°C to approximately 100°C.

Compounds of formula (IIIB) can be prepared from compounds of formula (IVB)

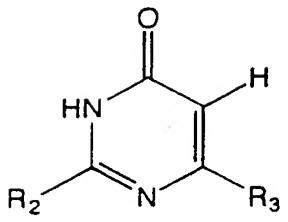
Formula IVB



wherein R^2 and R^3 are as hereinbefore defined and Z is a leaving group, with an amine NR'R" (wherein R' and R" are as defined for R^1) or a suitable derivative thereof. Suitable leaving groups include halogens such as bromine. The reaction is carried out in an organic solvent (e.g., dioxane, ethanol, N,N-dimethylformamide) or in neat amine at a temperature of approximately 20°C to approximately 100°C.

Compounds of formula (IVB) can be prepared from compounds of formula (VB)

Formula VB



wherein R^2 and R^3 are as hereinbefore defined by reaction with a halogenating reagent (e.g., bromine, N-bromosuccinimide, iodine monobromide, iodine monochloride or iodine) and optionally with a base (e.g., sodium hydride) in a suitable solvent (e.g., tetrahydrofuran, acetic acid, water) at a temperature of approximately 0° C to approximately 40° C.

Compounds of formula (VB) can be prepared by various methods known in the art or are available from commercial sources.

Specifically preferred intermediate compounds for synthesis of the above- listed specifically preferred compounds of Formula I are:

5-(Phenoxy)isocytosine
5-(4-Methylphenoxy)isocytosine
5-(4-Fluorophenoxy)isocytosine
5-(4-Chlorophenoxy)isocytosine
5-(4-Chlorophenoxy)uracil
2-Methoxy-5-(phenoxy)pyrimidin-4(3H)-one
5-(4-Chlorophenoxy)-2-(mercapto)pyrimidin-4(3H)-one
5-(4-Chlorophenoxy)-2-(methylthio)pyrimidin-4(3H)-one
5-(4-chlorophenoxy)-2-(4-methylpiperazino)pyrimidin-4(3H)-one
5-(4-chlorophenoxy)-2-(4-methylpiperazino)pyrimidin-4(3H)-one
5-(4-Chlorophenoxy)-2-(dimethylamino)pyrimidin-4(3H)-one

5-Benzyl-2,4-dichloropyrimidine

5-(3,4,5-Trimethoxybenzyl)isocytosine

5-Benzyl-2-(methylthio)pyrimidin-4(3H)-one

5-(4-Chlorobenzyl)isocytosine

5-(4-Isopropylbenzyl)isocytosine

5-(4-Methoxybenzyl)isocytosine

2-Methyl-5-(phenethyl)pyrimidin-4(3H)-one

5-(Phenethyl)isocytosine

5-(4-Methoxyphenethyl)isocytosine

5-(Phenylpropyl)isocytosine

2-Methyl-5-(phenylpropyl)pyrimidin-4(3H)-one

5-(4-Bromophenyl)isocytosine

5-(4-Fluorophenyl)isocytosine

5-(4-Chlorophenyl)isocytosine

2-Chloro-4-morpholino-5-(phenethyl)pyrimidine

5-Benzyl-2-chloro-4-(4-methylpiperazino)pyrimidine

5-Benzyl-2-chloro-4-(morpholino)pyrimidine

5-Benzyl-2-chloro-4-[2-(2-hydroxyethoxy)ethyl]pyrimidine

5-Benzyl-2-chloro-4-(4-hydroxypiperidino)pyrimidine

5-[4-(4-Chlorobenzyloxy)benzyl]isocytosine

5-(4-Methylbenzyl)isocytosine

5-[(3-Pyridyl)methyl]isocytosine

4-Chloro-2-morpholino-5-(phenethyl)pyrimidine

5-(Morpholino)isocytosine

5-(4-Methylpiperazino)isocytosine

5-(4-Methylpiperazino)pyrimidin-4(3H)-one

5-(4-Chlorophenethyl)isocytosine

5-(4-Chlorophenoxy)-2-morpholinopyrimidin-4(3H)-one

5-(4-Chloro-2-methylphenoxy)isocytosine

5-(4-Chlorophenoxy)pyrimidin-4(3H)-one

5-(4-Chlorophenoxy)-2,4-dichloropyrimidine

2-Chloro-5-(4-chlorophenoxy)-4-(4-methylpiperazino)pyrimidine

5-(4-Methylbenzyl)uracil

5-(4-Ethylphenoxy)isocytosine

5-(3-Chlorophenoxy)isocytosine

5-(3-Fluorophenoxy)isocytosine

5-(4-Chloro-2-fluorophenoxy)isocytosine

5-(2,4-Dichlorophenoxy)isocytosine

5-(2,3-Difluorophenoxy)isocytosine

5-(4-Trifluoromethoxyphenoxy)isocytosine

5-(2-Methylphenoxy)isocytosine

5-(3-Methylphenoxy)isocytosine

5-(4-Chlorophenoxy)-2-(4-fluoroanilino)pyrimidin-4(3H)-one

5-(4-Bromophenoxy)isocytosine

5-(2-Chlorophenoxy)isocytosine

5-(2-Methyloxyphenoxy)isocytosine

5-(3-Methyloxyphenoxy)isocytosine

5-(4-Methyloxyphenoxy)isocytosine

5-(4-Isopropylphenoxy)isocytosine

5-(4-Trifluoromethylphenoxy)isocytosine

5-(2,4-Difluorophenoxy)isocytosine

5-(3,4-Difluorophenoxy)isocytosine

5-(4-Chlorophenoxy)-2-(diisopropylaminomethyleneamino)pyrimidin-4(3H)-one

5-(4-Chlorophenoxy)-2-(diisopropylaminomethyleneamino)-4-(4-(2-hydroxyethyl)

piperazino)pyrimidine

5-(4-Chlorophenoxy)-2-(diisopropylaminomethyleneamino)-4-(2-(2-hydroxyethoxy)

ethylamino)pyrimidine

Esters and amides of compounds of Formula I can be made by reaction with a carbonylating agent (e.g., ethyl formate, acetic anhydride, methoxyacetyl chloride, benzoyl chloride, methyl isocyanate, ethyl chloroformate, methanesulfonyl chloride) and a suitable base (e.g., 4-dimethylaminopyridine, pyridine, triethylamine,

potassium carbonate) in a suitable organic solvent (e.g., tetrahydrofuran, acetone, methanol, pyridine, N,N-dimethylformamide) at a temperature of 0°C to 60° C.

Salts of the compounds of Formula I can be made from the free base form by reaction with the appropriate acid.

The following Examples illustrate the present invention but should not be construed as a limitation to the scope thereof.

Examples

Example 1
Preparation of 5-(4-chlorophenoxy)isocytosine

a) Preparation of ethyl 4-chlorophenoxyacetate

A solution of 4-chlorophenoxyacetic acid (Aldrich) (18.62 g, 99.8 mmoles) and concentrated sulfuric acid (Fisher) (2.5 mL) in ethanol (170 mL) was refluxed with stirring under a Drierite tube for 96 hours. The reaction solution was cooled in an ice-bath, and the volatiles were removed by spin evaporation in vacuo to a volume of about 100 mL. The liquid was dissolved in dichloromethane (225 mL) and washed with a solution of 5% aqueous sodium bicarbonate (4 X 100 mL) and finally with brine (1 X 50 mL). The solution was dried over sodium sulfate and spin evaporated in vacuo to give 19.97 g (93% yield) of ethyl 4-chlorophenoxyacetate as an amber liquid.

b) Preparation of 5-(4-chlorophenoxy)isocytosine

A solution of ethyl 4-chlorophenoxyacetate (19.90 g, 92.7 mmoles) and ethyl formate (Acros) (30 mL, 371 mmoles) in tetrahydrofuran (100 mL) was added dropwise to a stirred dispersion of sodium hydride (60 % dispersion in mineral oil) (Aldrich) (5.31 g, 132.7 mmoles) in tetrahydrofuran (50 mL). After 30 minutes, when about 60% of the solution had been added, the reaction was cooled with an ice-bath to slow the

reaction. After a total of 1 hour addition was complete, the addition funnel was rinsed with tetrahydrofuran (15 mL), and the reaction mixture was stirred at ambient temperature for 16 hours. The solution was cooled on an ice-bath and ethanol (11 mL) was added. The volatiles were removed by spin evaporation in vacuo to give the sodium salt of ethyl 2-formyl-2-(4-chlorophenoxy)acetate as a syrup that solidified after several hours. The solid was largely dissolved in ethanol (100 mL) and combined with a white mixture prepared from mixing sodium methoxide (Aldrich) (6.04 g, 106.2 mmoles) and guanidine carbonate (Aldrich) (10.05 g, 55.7 mmoles) in ethanol (75 mL). The reaction mixture was refluxed with stirring for 6 hours. The reaction mixture was cooled on an ice-bath, and the volatiles were removed by spin evaporation in vacuo to give a semi-solid residue, which was dissolved in cold water to a volume of 500 mL. The solution was vigorously stirred and carefully acidified to pH 5 with acetic acid (15 mL), which was added in 3 equal portions. The cream colored mixture was stirred for 2 hours. The solid was collected, washed extensively with water (750 mL), and vacuum suction air dried to give the crude solid. The solid was heated with stirring in ethanol to a final volume of 200 mL. The cooled mixture was collected, washed with ethanol and dried to give 16.83 g (76 % yield) of 5-(4-chlorophenoxy)isocytosine as a white solid, mp 245°C.

Example 2

Preparation of 2-amino-5-(4-chlorophenoxy)-4-(piperazino)pyrimidine

A solution of oxalyl chloride (Acros) (8.936 g, 70.4 mmoles) in dichloromethane (5 mL) was added in ten equal portions to a stirred, ice-bath cooled solution of diisopropylformamide (Aldrich) (10.057 g, 77.8 mmoles) in dichloromethane (300 mL). The ice-bath was removed, and the clear solution was stirred at ambient temperature for 40 minutes. Solid 5-(4-chlorophenoxy)isocytosine (6.022 g, 25.33 mmoles) was added, and the mixture was refluxed with stirring for 1 hour. The resultant solution was cooled and poured into an ice-bath cooled solution of vigorously stirred saturated aqueous sodium bicarbonate (400 mL). The layers were separated, and the organic phase was washed with ice cold water (200 mL), ice cold brine (100 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to give the intermediate chloropyrimidine as an unstable yellow

solid. The yellow solid was dissolved in ethanol (80 mL), and added to a solution of anhydrous piperazine (Acros) (40.29 g, 467.7 mmoles) in ethanol (110 mL). The reaction was refluxed with stirring for 20 hours. Sodium hydroxide pellets (Aldrich) (19.624 g, 490.6 mmoles) and water (75 mL) was added to the cooled solution, and the reaction was refluxed with stirring for 20 hours. The volatiles were removed by spin evaporation in vacuo to a volume of about 250 mL. This solution was diluted with portions of ice and cold water with vigorous stirring to a volume of 1 L. The solid material was collected, washed with ice water (2 X 100 mL), air dried by vacuum suction and dried at 75°C in vacuo to give 5.919 g (76% yield) of 2-amino-5-(4-chlorophenoxy)-4-(piperazino)pyrimidine as a white solid, mp 93-95°C.

Example 3

Preparation of 2-amino-5-(4-chlorophenoxy)-4-(4-formylpiperazino)pyrimidine

Ethyl formate (Acros) (11 mL) was added to a solution of 2-amino-5-(4-chlorophenoxy)-4-(piperazino)pyrimidine (0.433 g, 1.41 mmoles) in methanol, and after 16 hours the solution was spin evaporated in vacuo to give a colorless syrup. The syrup was triturated under hexanes containing 1% ethyl acetate to give a solid that was collected and recrystallized from ethyl acetate to give 0.250 g (53% yield) of 2-amino-5-(4-chlorophenoxy)-4-(4-formylpiperazino)pyrimidine as white crystals, mp 159-161°C.

Example 4

Preparation of 2-amino-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine

A solution of oxalyl chloride (Acros) (2.267 g, 17.86 mmoles) in dichloromethane (5 mL) was added in several portions to a stirred, ice-bath cooled solution of diisopropylformamide (Aldrich) (2.522 g, 19.52 mmoles) in dichloromethane (65 mL). The ice-bath was removed, and the clear solution was stirred at ambient temperature for 50 minutes. Solid 5-(4-chlorophenoxy)isocytosine (1.030 g, 4.33 mmoles) was added with dichloromethane (20 mL), and the mixture was refluxed with stirring for 0.5 hour. The resultant solution was cooled and poured into an ice-bath cooled

solution of vigorously stirred, saturated aqueous sodium bicarbonate (300 mL). The layers were separated, and the organic phase was washed with ice cold water (3 X 100 mL), ice cold brine (100 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to give the intermediate chloropyrimidine as a syrup. The syrup was dissolved in ethanol (100 mL), 1-(2-hydroxyethyl)piperazine (Aldrich) (5.07 g, 38.94 mmoles) and ethanol (40 mL) were added, and the reaction was refluxed with stirring for 45 hours. Sodium hydroxide pellets (Aldrich) (5.68 g, 142 mmoles) and water (150 mL) were added to the cooled solution, and the reaction was refluxed with stirring for 2 hours. The volatiles were removed by spin evaporation in vacuo to a small volume, and the residue was dissolved in dichloromethane containing 5% ethanol (250 mL). The solution was washed with water (6 X 100 mL) until the washings were neutral to pH paper, brine (100 mL) and then dried over sodium sulfate. The dry solution was spin evaporate in vacuo to give a white solid that was recrystallized from ethylacetate to give 0.449 g (29% yield) of 2-amino-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine as a white powder, mp 121-123°C.

Example 5

Preparation of 2-amino-5-(4-chlorophenoxy)-4-(4-methylpiperazino)pyrimidine

A solution of oxalyl chloride (Acros) (1.111 g, 8.75 mmoles) in dichloromethane (5 mL) was added in several portions to a stirred, ice-bath cooled solution of diisopropylformamide (Aldrich) (1.306 g, 10.10 mmoles) in dichloromethane (75 mL). The ice-bath was removed, and the clear solution was stirred at ambient temperature for 30 minutes. Solid 5-(4-chlorophenoxy)-isocytosine (0.518 g, 2.18 mmoles) was added, and the mixture was refluxed with stirring for 0.5 hour. The resultant solution was cooled and poured into an ice-bath cooled solution of vigorously stirred, saturated aqueous sodium bicarbonate (200 mL). The layers were separated, and the aquous layer was extracted with dichloromethane (60 mL). The combined organic layers were washed with ice cold water (2 X 100 mL), ice cold brine (100 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to give the intermediate chloropyrimidine as a yellow liquid. The liquid was dissolved in ethanol (100 mL), 1-methylpiperazine (Aldrich) (3.723 g, 37.10 mmoles)

was added, and the reaction was refluxed with stirring for 19 hours. Sodium hydroxide pellets (Aldrich) (3.30 g, 82.5 mmoles) and water (100 mL) was added to the cooled solution, and the reaction was refluxed with stirring for 4 hours. The volatiles were removed by spin evaporation in vacuo to a small volume, and the residue was dissolved in dichloromethane (200 mL). The solution was washed with water (5 X 100 mL) until the washings were neutral to pH paper, brine (100 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to give a clear liquid that was dissolved in ethyl acetate (5 mL). The resultant colorless crystals were collected and dried to give 0.107 g (15% yield) of 2-amino-5-(4-chlorophenoxy)-4-(4-methylpiperazino)pyrimidine as a white powder, mp 143-144°C.

Example 6

Preparation of 2-amino-5-(4-chlorophenoxy)-4-(2-(2-hydroxyethoxy)ethylamino)pyrimidine hydrochloride

A solution of oxalyl chloride (Acros) (0.961 g, 7.57 mmoles) in dichloromethane (5 mL) was added in several portions to a stirred, ice-bath cooled solution of diisopropylformamide (Aldrich) (1.177 g, 9.11 mmoles) in dichloromethane (35 mL). The ice-bath was removed, and the clear solution was stirred at ambient temperature for 50 minutes. Solid 5-(4-chlorophenoxy)-isocytosine (0.562 g, 2.36 mmoles) and dichloromethane (35 mL) was added, and the mixture was refluxed with stirring for 1 hour. The resultant solution was cooled and poured into an ice-bath cooled solution of vigorously stirred, saturated aqueous sodium bicarbonate (200 mL). The layers were separated, and the organic phase was washed with ice cold water (100 mL), ice cold brine (50 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to give the intermediate chloropyrimidine as a yellow liquid. The liquid was dissolved in ethanol (25 mL) and 2-(2-aminoethoxy)ethanol (Acros) (4.75 g, 45.18 mmoles) and ethanol (10 mL) were added. The reaction was refluxed with stirring for 21 hours. Sodium hydroxide pellets (Aldrich) (2.45 g, 61.25 mmoles) and water (25 mL) was added to the cooled solution, and the reaction was refluxed with stirring for 44 hours. The volatiles were removed by spin evaporate in vacuo to a small volume, and the residue was partioned between dichloromethane (100 mL) and water (40 mL). The layers were separated, and the dichloromethane solution

was washed with water (6 X 40 mL) until the washings were neutral to pH paper, brine (80 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to a clear liquid. The liquid was dissolved in ethanol (50 mL), 37% hydrochloric acid (3 mL) was added, and the solution was spin evaporated in vacuo to give a light brown oil. The oil was triturated under ethyl ether to give a solid that was collected and recrystallized from acetone-ethanol to give 0.177 g (20% yield) of 2-amino-5-(4-chlorophenoxy)-4-(2-(2-hydroxyethoxy)ethylamino)pyrimidine hydrochloride as beige crystals, mp 140-141°C.

Example 7

Preparation of 2-amino-4-(4-carbamoylpiperidino)-5-(4-chlorophenoxy)pyrimidine

A solution of oxalyl chloride (Acros) (1.103 g, 8.69 mmoles) in dichloromethane (5 mL) was added in several equal portions to a stirred, ice-bath cooled solution of diisopropylformamide (Aldrich) (1.345 g, 10.41 mmoles) in dichloromethane (95 mL). The ice-bath was removed, and the clear solution was stirred at ambient temperature for 45 minutes. Solid 5-(4-chlorophenoxy)isocytosine (1.04 g, 4.37 mmoles) was added, and the mixture was refluxed with stirring for 1.25 hours. The resultant solution was cooled and poured into an ice-bath cooled solution of vigorously stirred saturated aqueous sodium bicarbonate (350 mL). The layers were separated, and the organic phase was washed with ice cold water (100 mL), ice cold brine (75 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to give the intermediate chloropyrimidine as a yellow residue. This residue was dissolved in methanol (90 mL), combined with isonipecotamide (Aldrich) (4.150 g, 31.4 mmoles) in methanol (10 mL) and refluxed with stirring for 20 hours. Sodium hydroxide pellets (Aldrich) (1.093 g, 27.3 mmoles) and water (150 mL) were added to the cooled solution. The reaction was refluxed with stirring for 3 hours. The hot solution was filtered through flutted filter paper, seeded, and allowed to cool. The white clumps of crystals that formed were collected and washed with methanol-water:1-1 (40 mL) and water. Recrystallization from ethyl acetate-ethanol gave 0.263 g (17%) of 2-amino-4-(4-carbamoylpiperidine)-5-(4-chlorophenoxy)pyrimidine as colorless crystals, mp 208-211°C.

Example 8

Preparation of 2-amino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine

A solution of oxalyl chloride (Acros) (3.768 g, 29.68 mmoles) in dichloromethane (10 mL) was added in several equal portions to a stirred, ice-bath cooled solution of N-formylmorpholine (Acros) (3.944 g, 34.26 mmoles) in dichloromethane (100 mL). The ice-bath was removed, and the reaction was stirred at ambient temperature for 90 minutes. Solid 5-(4-chlorophenoxy)isocytosine (2.31 g, 9.72 mmoles) and dichloromethane (150 mL) was added, and the mixture was refluxed with stirring for 1.5 hour. The volatiles were removed by spin evaporated in vacuo to give a dark red oil, which was dissolved in methanol (100 mL) and combined with morpholine (Acros) (6.01 g, 68.98 mmoles). The reaction was refluxed with stirring for 3 hours. Sodium hydroxide pellets (Aldrich) (5.01 g, 125 mmoles) and water (60 mL) was added to the cooled solution, and the reaction was refluxed with stirring for 26 hours. The solution was diluted with water (60 mL), and the volatiles were removed by spin evaporate in vacuo to a volume of about 100 mL. The solid was collected, washed with water and air dried by vacuum suction to give a white solid. This material was recrystallized from methanol-water to give 1.433 g (48% yield) of 2-amino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine as white pins, mp 138-140°C.

Example 9

Preparation of 4-(4-acetylpiperazino)-2-amino-5-(4-chlorophenoxy)pyrimidine

Acetic anhydride (Aldrich) (0.318 g, 3.11 mmoles) in tetrahydrofuran (1.5 mL) was added to a solution of 2-amino-5-(4-chlorophenoxy)-4-(piperazino)pyrimidine (0.511 g, 1.67 mmoles) and triethylamine (0.526 g, 5.20 mmoles) in tetrahydrofuran (13 mL). After 0.5 hours the solution was diluted with ice water (40 mL) and poured into dichloromethane (75 mL). The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate (40 mL), brine (40 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to give a white foam. The foam was recrystallized from hexanes-ethyl acetate to give 0.348 g (60% yield) of 4-(4-acetylpiperazino)-2-amino-5-(4-chlorophenoxy)pyrimidine as beige pins, mp 153-157°C.

Example 10

Preparation of 5-(4-chlorophenoxy)-4-morpholino-2-(3-phenylureido)pyrimidine

Phenylisocyanate (0.24 g, 2.01 mmoles) in acetone (1 mL) was added to a stirred solution of 2-amino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine (0.485 g, 1.58 mmoles) in tetrahydrofuran (11 mL), which was cooled on an ice-bath. After 16 hours the white crystals were collected, washed with a few mL of ethyl acetate and with hexanes, and dried to give 0.271 g (40 % yield) of 5-(4-chlorophenoxy)-4-morpholino-2-(3-phenylureido)pyrimidine as a white solid, mp 229-231°C.

Example 11

Preparation of 2-amino-5-benzyl-4-(dimethylamino)pyrimidine

This compound was prepared in an analogous manner to that of Example 6 with replacement of diisopropylformamide with dimethylformamide (Aldrich). The reaction mixture was cooled to give crystalline product which was collected, washed with water and dried to give 2-amino-5-benzyl-4-(dimethylamino)pyrimidine as white crystals, mp 181-182°C.

Example 12

Preparation of 5-benzyl-4-[2-(2-hydroxyethoxy)ethylamino]pyrimidine

A mixture of 5-benzyl-2-chloro-4-[2-(2-hydroxyethoxy)ethylamino]pyrimidine (3.50 g, 12.08 mmoles), ethanol (190 mL) and 10% Pd on carbon (Aldrich) (0.84 g) was shaken in the presence of hydrogen at 2-3 atm for 17 hours. The reaction mixture was filtered through a pad of Celite, and the filtrates were spin evaporated in vacuo. The residual syrup was dissolved in dichloromethane (40 mL) and washed with water (20 mL), brine (20 mL) and then dried over sodium sulfate. The dry solution was spin evaporated in vacuo to give a residue that was triturated under hexanes to give 0.15 g (5 % yield) of 5-benzyl-4-[2-(2-hydroxyethoxy)ethylamino]pyrimidine as a white solid, mp 86-87°C.

Example 13

Preparation of 5-(4-chlorophenoxy)-2-(methylmercapto)pyrimidin-4(3H)-one

Iodomethane (Aldrich) (2.8 mL, 45 mmoles) was added to a solution of 5-(4-chlorophenoxy)-2-(mercapto)pyrimidin-4(3H)-one (10.24 g, 40 mmoles) in methanol (52 mL) and 1.0 N aqueous sodium hydroxide (40 mL). The resultant mixture was stirred at ambient temperature for 5.5 hours, then heated at 60°C for 30 minutes. The mixture was spin evaporated in vacuo to give a solid, which was triturated with ice-water and then collected by suction filtration. Half of the light brown solid was recrystallized from ethyl acetate and half from ethanol to give 7.06 g (66% yield) of 5-(4-chlorophenoxy)-2-(methylmercapto)pyrimidin-4(3H)-one as a fluffy off-white solid, mp 232-233°C.

Example 14

Preparation of 5-(4-chlorophenoxy)-2-(4-methylpiperazino)pyrimidin-4(3H)-one

A solution of of 5-(4-chlorophenoxy)-2-(methylmercapto)pyrimidin-4(3H)-one (1.58 g, 5.87 mmoles) and 1-methylpiperazine (Aldrich) (6.1 mL, 55 mmoles) was heated at 135°C for 18 hours. The dark brown mixture was spin evaporated in vacuo. The residue was dissolved in ethyl acetate and applied to a column (d = 5 cm) of Silica Gel 60 that was equilibrated with ethyl acetate. The column was eluted with ethyl acetate by flash chromatography to remove unreacted starting material. Elution with 10% methanol-dichloromethane and spin evaporation in vacuo of the combined fractions gave a beige solid that was triturated with ethyl acetate to give 0.70 g (37% yield) of 5-(4-chlorophenoxy)-2-(4-methylpiperazino)pyrimidin-4(3H)-one. Recrystallization from ethyl acetate gave off-white flakes that had an NMR spectrum consistent with the assigned structure.

Example 15

Preparation of 5-benzyl-2,4-(dimorpholino)pyrimidine

A mixture of 5-benzyluracil (39.0 g, 193 mmoles) and phosphorus oxychloride (Aldrich) (280 g, 1.82 moles) was refluxed with stirring under a Drierite tube for 2.5

hours. The cooled reaction mixture was slowly poured into a stirred mixture of crushed ice and diethyl ether (100 mL). After the mixture warmed to ambient temperature additional diethyl ether (200 mL) was added, and the mixture was stirred for 10 minutes. The ether layer was separated, filtered to remove insoluble starting material, and then washed with saturated aqueous sodium bicarbonate (3 X 100 mL). The solution was dried over calcium chloride, filtered and spin evaporated in vacuo to give 35.43 g (76% yield) of the intermediate 5-benzyl-2,4-dichloropyrimidine as a syrup, which was used without further purification. A solution of crude 5-benzyl-2,4-dichloropyrimidine (9.76 g, 40.6 mmoles) and morpholine (13.0 g, 150 mmoles) in ethanol (55 mL) was stirred at ambient temperature for 21 hours. The solution was cooled in an ice-bath, and the resultant precipitate was removed by suction filtration. The filtrate was spin evaporated in vacuo to give a syrup that solidified. The solid was triturated for 3 hours with diethyl ether (200 mL) and collected by suction filtration. Recrystallization from ethanol, 2-propanol, and finally methanol gave 2.03 g (14 % yield) of 5-benzyl-2,4-(dimorpholino)pyrimidine, mp 123-124°C.

EXAMPLE 16

a) Preparation of ethyl 4-chloro-2-fluorophenoxyacetate

A mixture of 4-chloro-2-fluorophenol (Aldrich) (5.00 g, 33.78 mmoles), anhydrous potassium
carbonate (Aldrich) (7.20 g, 52.10 mmoles), ethyl bromoacetate (Aldrich) (5.41 g, 31.74 mmoles)
and dry acetone (Aldrich) (80 mL) was refluxed with stirring under a Drierite tube for 21 hours.
The reaction was cooled, and the volatiles were removed by spin evaporation in vacuo. The
white residue was partitioned between ice cold water (150 mL) and dichloromethane (150 mL).

The dichloromethane phase was separated and washed with ice cold water (2 X 50 mL), an ice cold solution of 5% aqueous sodium hydroxide (50 mL) and finally with ice cold water (2 X 50 mL). The dichloromethane solution was dried over sodium sulfate and spin evaporated in vacuo to give a quantitative yield of ethyl 4-chloro-2-fluorophenoxyacetate as a clear liquid.

Example 17

Preparation of 2-amino-5-(4-chlorophenoxy)-4-(4-(2-pivaloyloxyethyl)piperazino)pyrimidine

A solution of trimethylacetyl chloride (Aldrich) (0.063 g, 0.52 mmoles) in of dry dichloromethane (3 mL) was added to a stirred, ice bath cooled solution of 2-amino-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl) piperazino) pyrimidine (0.185 g, 0.5 mmoles) in dichloromethane (5 mL). Solid 4-dimethylaminopyridine (Aldrich) (0.061 g, 0.5 mmoles) was added to the mixture, and the resultant solution was stirred on an ice bath for 4.5 hours. The reaction solution was diluted with additional dichloromethane (50 mL) and washed with 5% aqueous sodium bicarbonate (2 X 25 mL) and water (2 X 25 mL) . The organic phase was dried over sodium sulfate and spin evaporated in vacuo to give 0.15 g of a white solid. The solid was dissolved in ethyl acetate and applied to a column of silica gel 60 (230-400 mesh) prepared for flash chromatography in ethyl acetate. The column was eluted with

ethyl acetate, and the solvent was spin evaporated in vacuo to give a white solid that was recrystallized from dichloromethane-hexanes to give 0.088 g (40% yield) of 2-amino-5-(4-chlorophenoxy)-4-(4-(2-pivaloyloxyethyl)piperazino)pyrimidine as white needles, mp 123-125°C.

Example 18

Preparation of 2-chloro-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine

A solution of 5-benzyl-2,4-dichloropyrimidine (9.66 g, 38 mmoles), triethylamine (Aldrich) (4.15 g, 41 mmoles), and ethanol (20 mL) was stirred at ice bath temperature for 10 minutes. 1-Methylpiperazine (Aldrich) (3.83 g, 38 mmoles) in ethanol (10 mL) was added, and the reaction was stirred at ambient temperature for 16 hours. The solution was spin evaporated in vacuo at 40°C to give a residue that was partitioned between dichloromethane (50 mL) and water (70 mL). The dichloromethane phase was separated and washed with water (2 X 7 mL), and finally with brine (50 mL). The dichloromethane solution was dried over sodium sulfate, filtered and applied to a column (4 X 20 cm) of Silica Gel 60 (230-400 mesh) that was equilibrated with dichloromethane. The column was eluted with dichloromethane (400 mL) by flash chromatography to remove impurities. The product was eluted with 2% methanol-dichloromethane, and the combined fractions were spin evaporated in vacuo to give 9.89 g (cc% yield) of 2-chloro-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine.

Example 19

Preparation of 2-(2-hydroxyethoxy)ethylamino)-5-(4-methylbenzyl)-4-(4-methyl piperazino)pyrimidine

A solution of 2-chloro-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine (1.46 g, cc mmoles), 2-propanol (25 mL) and 2-(2-aminoethoxy)ethanol (4.79 g, 46 mmoles) was heated in a stainless steel reaction vessel at 155°C for 16 hours. The vessel contents were spin evaporated in vacuo at 60°C to give a residue that was partitioned between dichloromethane (35 mL) and water (150 mL). The dichloromethane phase was separated and washed with water (150 mL), and finally with brine (100 mL). The solution was dried over sodium sulfate, filtered, and spin evaporaed in vacuo to give a syrup. The syrup was dissolved in 2-propanol (20 mL), 37% hydrochloric acid (15 drops) was added, and the solution was spin evaporated in vacuo. The residue was crystallized from methanol (2 mL) to give 0.34 g of 2-(2-hydroxyethoxy)ethylamino)-5-(4-methylbenzyl)-4-(4-methyl piperazino)pyrimidine as carmel colored crystals, mp 207-209°C.

The following compounds were prepared by methods similar to those of the indicated Examples

Chemical Name	MP°C	Ex. No.
2-Amino-4-morpholino-5-(phenoxy)pyrimidine	168-170	1, 8
2-Amino-5-(4-methylphenoxy)-4-(morpholino)pyrimidine	145-147	1,8
2-Amino-5-(4-fluorophenoxy)-4-(morpholino)pyrimidine	123-125	1,8
2-Amino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine	138-140	1,8
2-Amino-5-(4-chlorobenzyloxy)-4-(morpholino)pyrimidine		1,8
2-Amino-5-(benzyloxy)-4-(morpholino)pyrimidine		1,8
2-Amino-5-(4-chlorophenoxy)-4-(2-(2-hydroxyethoxy)-ethylamino)pyrimidine HCl	140-141	1,6
2-Amino-4-(4-carbamoylpiperidino)-5-(4-chlorophenoxy)-pyrimidine	208-211	1,7
2-Amino-5-(4-chlorophenoxy)-4-(piperazino)pyrimidine	93-95	1,2
2-Amino-5-(4-chlorophenoxy)-4-(4-methylpiperazino)-pyrimidine	143-144	1,5
2-Amino-5-(4-chlorophenoxy)-4-(4-ethylpiperazino)-pyrimidine	129-131	1,5
2-Amino-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)-piperazino)pyrimidine	120-135	1,4
2-Amino-5-(4-fluorophenoxy)-4-(4-phenylpiperazino)-pyrimidine	219-222	1,4
2-Amino-5-(4-chlorophenoxy)-4-(4-phenylpiperazino)-pyrimidine	186-187	1,4
2-Amino-5-(4-chlorophenoxy)-4-(4-(2-pyridyl)piperazino)-pyrimidine	123-124	1,4
2-Amino-4-(4-benzylpiperazino)-5-(4-chlorophenoxy)-pyrimidine	119-120	1,4

2-Amino-5-(4-chlorophenoxy)-4-(4-formylpiperazino)-
pyrimidine 159-161
1,2,3
4-(4-Acetylpiperazino)-2-amino-5-(4-chlorophenoxy)-
pyrimidine 153-157
1,2,9 2-Amino-5-(4-chlorophenoxy)-4-(4-methoxyacetylpiperazino)-
pyrimidine 148-150
1,2,9
2-Anilino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine
13,14,8
5-(4-Chlorophenoxy)-2-(dimethylamino)-4-(4-methylpiperazino)-
pyrimidine 165-170 1,4
5-(4-Chlorophenoxy)-4-morpholino-2-(3-phenylureido)-
pyrimidine 229-231
1,8,10
5-(4-Chlorophenoxy)-2,4-(dimorpholino)pyrimidine 150-151
13,14,4
5-(4-Chlorophenoxy)-2-(4-methylpiperazino)-4-(morpholino)-
pyrimidine HCl 209-210
13,14,6
5-(4-Chlorophenoxy)-4-(4-methylpiperazino)-2-(morpholino)-
pyrimidine 259-260
13,14,5
5-(4-Chlorophenoxy)-4-[4-(2-hydroxyethyl)piperazino]-2-(morpholino)-
pyrimidine
13,14,4

2-Amino-5-benzyl-4-(morpholino)pyrimidine 206-207 1,8
2-Amino-5-benzyl-4-(dimethylamino)pyrimidine 181-182
1,11
2-Amino-5-(4-methoxybenzyl)-4-(morpholino)pyrimidine 136-137
1,8

5-Benzyl-4-[2-(2-hydroxyethoxy)ethylamino]pyrimidine	86-87	15,12	
2-Amino-5-benzyl-4-(4-hydroxypiperidino)pyrimidine	145-146	1,4	
2-Amino-5-benzyl-4-(4-methylpiperazinoamino)-pyrimidine	184-185	1,4	
2-Amino-5-benzyl-4-(4-carbamoylpiperidino)pyrimidine	217-218	1,7	
2-Amino-5-benzyl-4-(4-methylpiperazino)pyrimidine	174-175	1,4	
2-Amino-5-benzyl-4-(4-hydroxyethylpiperazino)-pyrimidine	161-162	1,4	
5-Benzyl-2,4-bis(4-methylpiperazino)pyrimidine		15	
5-Benzyl-2,4-(dimorpholino)pyrimidine	123-124	15	
5-Benzyl-2-dimethylamino-4-(4-methylpiperazino)-pyrimidine HCl		1,6	
2-Amino-5-(4-methylbenzyl)-4-(4-methylpiperazino)-pyrimidine	185-186	1,5	
2-Amino-4-(4-ethylpiperazino)-5-(4-methylbenzyl)pyrimidine	115-116	1,5	
2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-methylbenzyl)-pyrimidine	122-124	1,4	
2-Amino-4-(4-hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine	153-154	1,4	
2-Amino-5-(4-chlorobenzy)-4-(morpholino)pyrimidine	181-183	1,8	
2-Amino-4-[2-(2-hydroxyethyl)ethylamino]-5-(4-chlorobenzyl)-pyrimidine	59-60	1,5	
2-Amino-5-(4-chlorobenzyl)-4-(4-methylpiperazino)pyrimidine	194-195	1,5	
2-Amino-5-(4-chlorobenzyl)-4-(4-ethylpiperazino)pyrimidine	157-161	1,5	

2-Amino-5-(4-chlorobenzyl)-4-(4-hydroxyethylpiperazino)-pyrimidine 98-99 1,4

2-Amino-5-(4-chlorobenzyl)-4-(4-hydroxypiperidino)pyrimidine 183-184 1,4

2-Amino-5-(4-methoxybenzyl)-4-(4-methylpiperazino)pyrimidine 157-158 1,5

2-Amino-5-(4-hydroxybenzyl)-4-(4-methylpiperazino)-pyrimidine HCl 155-156 1,6

2-Amino-4-(4-methylpiperazino)-5-(isopropylbenzyl)pyrimidine 179-181 1,5

2-Amino-4-(4-ethylpiperazino)-5-(4-isopropylbenzyl)pyrimidine 149-150 1,5

2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-isopropylbenzyl)-pyrimidine 136-137 1,4

2-Amino-5-(4-hydroxypiperidino)-4-(4-isopropylbenzyl)pyrimidine 146-148 1,4

2-Amino-4-(4-methylpiperazino)-5-(3,4,5-trimethoxybenzyl)-pyrimidine 190-192 1,5

2-Amino-4-(4-ethylpiperazino)-5-(3,4,5-trimethoxybenzyl)-pyrimidine 160-161 1,5

2-Amino-4-(4-hydroxyethylpiperazino)-5-(3,4,5-trimethoxybenzyl)-pyrimidine 155-157 1,4

2-Amino-4-(4-hydroxypiperidino)-5-(3,4,5-trimethoxybenzyl)-pyrimidine 164-165 1,4

2-Amino-4-(4-methylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)-pyrimidine 171-172 1,5

2-Amino-4-(4-ethylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)-pyrimidine 149-150 1,5

2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)-pyrimidine 155-156 1,4

2-Amino-4-(4-methylpiperazino)-5-((3-pyridyl)methyl)pyrimidine 174-175 1,5

2-Amino-4-(4-ethylpiperazino)-5-[(3-pyridyl)methyl]pyrimidine	160-161		
1,5			
2-Amino-4-(4-hydroxyethylpiperazino)-5-([3-pyridyl]methyl)-pyrimidine	144-145	1,4	
4-Anilino-2-methyl-5-(phenethyl)pyrimidine	133-134	1,4	
4-Benzylamino-2-methyl-5-(phenethyl)pyrimidine	116-117	1,4	
4-[2-(2-Hydroxyethoxy)ethylamino]-2-methyl-5-(phenethyl)-pyrimidine	85-86	1,4	
2-Methyl-4-morpholino-5-(phenethyl)pyrimidine	48-49		
1,8			
2,4-Dimorpholino-5-(phenethyl)pyrimidine	70-72	15	
2-Amino-4-morpholino-5-(phenethyl)pyrimidine	116-117		
1,8			
4-Morpholino-5-(phenethyl)pyrimidine HCl	243-244		
15,12			
2-Amino-5-(4-methoxyphenethyl)-4-(morpholino)pyrimidine	123-124	1,8	
2-Amino-4-morpholino-5-(phenylpropyl)pyrimidine	105-106	1,8	
2-Amino-4-morpholino-5-(phenyl)pyrimidine	174-175	1,8	
2-Amino-5-(4-fluorophenyl)-4-(morpholino)pyrimidine	202-203		
1,8			
2-Amino-5-(4-chlorophenyl)-4-(morpholino)pyrimidine	235-237		
1,8			
2-Amino-5-(4-bromophenyl)-4-(morpholino)pyrimidine	228-229		
1,8			
2-Amino-5-(4-ethylphenoxy)-4-(4-methylpiperazino)pyrimidine	118-119		
16,1,5			
2-Amino-5-(2,4-dichlorophenoxy)-4-(4-methylpiperazino) pyrimidine	142-145		
16,1,5			
2-Amino-5-(4-chloro-2-methylphenoxy)-4-(4-methylpiperazino) pyrimidine	114-115		
16,1,5			
2-Amino-5-(3-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)			

pyrimidine 128-129

16,1,5

2-Amino-5-(2-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)

pyrimidine 111-112

16,1,4

2-Amino-5-(4-bromophenoxy)-4-(4-(2-hydroxyethyl)piperazino)

pyrimidine 130-131

16,1,4

2-Amino-5-(4-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)

pyrimidine 111-112

16,1,4

2-Amino-5-(3-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-trifluoromethyl

phenoxy)pyrimidine 157-158

16,1,4

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-methylphenoxy)

pyrimidine 98-99

16,1,4

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(3-methylphenoxy)

pyrimidine 114-115

16,1,4

2-Amino-4-(4-(2-hydroxyethyl)piperazino-5-(2-methylphenoxy))

pyrimidine 113-114

16,1,4

2-Amino-5-(4-ethylphenoxy)-4-(4-(2-hydroxyethyl)piperazino)

pyrimidine 105-107

16,1,4

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-isopropylphenoxy)

pyrimidine 118-119

16,1,4

2-Amino-5-(4-butylphenoxy)-4-(4-(2-hydroxyethyl)piperazino)

pyrimidine 139-140

16,1,4

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-methoxyphenoxy)
pyrimidine 94-95
16,1,4
2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(3-methoxyphenoxy)
pyrimidine 123-124
16,1,4
2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(2-methoxyphenoxy)
pyrimidine 114-115
16,1,4
2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-(trifluoromethoxy)
phenoxy)pyrimidine 131-132
16,1,4
2-Amino-5-(2,4-dichlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 170-173
16,1,4
2-Amino-5-(2,3-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 117-118
16,1,4
2-Amino-5-(2,4-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 110-111
16,1,4
2-Amino-5-(2,6-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 114-115
16,1,4
2-Amino-5-(3,5-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 137-138
16,1,4
2-Amino-5-(4-chloro-2-fluorophenoxy)-4-(4-(2-hydroxyethyl)
piperazino)pyrimidine 129-133
16,1,4
2-Amino-5-(2-chloro-4-fluorophenoxy)-4-(4-(2-hydroxyethyl)
piperazino)pyrimidine 139-140
16,1,4

2-Amino-5-(4-chloro-2-methylphenoxy)-4-(4-(2-hydroxyethyl)
piperazino)pyrimidine 171-172
16,1,4
2-Amino-5-(4-chlorophenoxy)-4-(4-(2-pivaloyloxyethyl)piperazino)
pyrimidine 123-125
1,4,17
2-Amino-4-(4-butyrylpiperazino)-5-(4-chlorophenoxy)
pyrimidine 132-142
1,5,9
2-Amino-5-(4-chlorophenoxy)-4-(4-phenoxyacetylpiperazino)
pyrimidine 126-127
1,5,9
2-Amino-4-(4-benzoylpiperazino)-5-(4-chlorophenoxy)
pyrimidine 162-167
1,5,9
2-Amino-5-(4-chlorophenoxy)-4-(4-ethoxycarbonylpiperazino)
pyrimidine 121-123
1,5,9
2-Amino-5-(4-chlorophenoxy)-4-(4-phenoxycarbonylpiperazino)
pyrimidine 128-130
1,5,9
2-Amino-5-(4-chlorophenoxy)-4-(4-methoxydicarbonylpiperazino)
pyrimidine HCl 182-185
1,5,9
2-Amino-4-(4-(3-carbamoylpropionyl)piperazino)-5-(4-chlorophenoxy)
pyrimidine 115-119
1,5,9
2-Amino-4-(4-(3-carboxypropionyl)piperazino)-5-(4-chlorophenoxy)
pyrimidine 117-119
1,5,9
2-Amino-5-(4-chlorophenoxy)-4-(4-(methlysulfonyl)piperazino)
pyrimidine 65-70
1,5,9

2-Amino-5-(4-chlorophenoxy)-4-(4-(phenylsulfonyl)piperazino)
pyrimidine <60
1,5,9
5-(4-Chlorophenoxy)-4-(4-methylpiperazino)-2-(1-pyrrolidinyl)
pyrimidine 112-113
13,14,5
2-(Anilino)-5-(4-chlorophenoxy)-4-(4-methylpiperazino)
pyrimidine
13,14,5
5-(4-Chlorophenoxy)-2-(4-fluoroanilino)-4-(4-methylpiperazino)
pyrimidine 2HCl 267-268
13,14,6
2-(Benzylamine)-5-(4-chlorophenoxy)-4-(4-methylpiperazino)
pyrimidine 93-94
13,14,5
2,4-Bis(4-ethylpiperazino)-5-(4-chlorophenoxy)
pyrimidine 2HCl 267-268
13,14,6
5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-
2-(isopropylamino)pyrimidine 2HCl 254-256
13,14,6
5-(4-Chlorophenoxy)-2-((2-hydroxyethyl)amino)-4-(4-(2-hydroxyethyl)
piperazino)pyrimidine maleate 155-164
13,14,6
5-(4-Chlorophenoxy)-2-(2-(2-hydroxyethoxy)ethylamino)-4-(4-
(2-hydroxyethyl)piperazino)pyrimidine HCl 134-135
13,14,6
2-(Anilino)-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 122-123
13,14,4
5-(4-Chlorophenoxy)-2-(4-fluoroanilino)-4-(4-(2-hydroxyethyl)
piperazino)pyrimidine HCl 192-195
13,14,6

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-
2-(4-methylanilino)pyrimidine 155-156
13,14,4
5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-
2-(1-pyrrolidinyl)pyrimidine 110-111
13,14,4
5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(piperidino)
pyrimidine 2HCL 227-232
13,14,6
5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-
2-(4-hydroxypiperidino)pyrimidine 2HCl 262 (dec)
13,14,6
5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-
2-(4-phenylpiperazino)pyrimidine 3HCl 236-245
(dec) 13,14,6
5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-
2-(4-methylpiperazino)pyrimidine 3HCl 280 (dec)
13,14,6
5-(4-Chlorophenoxy)-2-(4-ethylpiperazino)-4-(4-(2-
hydroxyethyl)piperazino)pyrimidine 3HCl 245-248
13,14,6
2,4-Bis(4-(2-hydroxyethyl)piperazino)-5-(4-chlorophenoxy)
pyrimidine 2hcl 243-244
13,14,6
2-Chloro-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 95-96 15
5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine HCl 180-181 1,4
5-(4-Chlorophenoxy)-4-(4-methylpiperazino)pyrimidine 155-157
1,5
2-Amino-5-(4-chlorophenyl)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 203-204 1,4

2-Amino-5-(4-chlorophenyl)-4-(4-methylpiperazino)pyrimidine 185-186
1,5
2-Amino-5-(4-fluorobenzyl)-4-(4-methylpiperazino)pyrimidine 182-184
1,5
2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-trifluoromethylbenzyl)
pyrimidine 154-155 1,4
2-(4-Carbamoylpiperidino)-5-(4-methylbenzyl)-4-(4-
methylpiperazino)pyrimidine 179-180
18,19
2-(2-Hydroxyethoxy)ethylamino)-5-(4-methylbenzyl)-4-(4-methyl
piperazino)pyrimidine 207-209
18,19
2-Amino-5-(4-chlorophenethyl)-4-(4-methylpiperazino)pyrimidine 159-160
1,5
2-Amino-5-(4-chlorophenethyl)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 123-124 1,4
2-Amino-5-(4-chlorobenzyloxy)-4-(4-methylpiperazino)pyrimidine167-168
16,1,5
2-Amino-5-(4-chlorobenzyloxy)-4-(4-(2-hydroxyethyl)piperazino)
pyrimidine 178-179
16,1,4
2-Amino-5-(4-chlorophenoxy)-4-(4-hydroxypiperidino)pyrimidine 146-147
1,5
2-Amino-4-(4-hydroxypiperidino)-5-(4-methylphenoxy)pyrimidine 148-151
1,5
2-Amino-5-(2,4-dichlorophenoxy)-4-(4-hydroxypiperidino)
pyrimidine HCl 247-252 1,6
5-(4-Chlorophenoxy)-4-(4-hydroxypiperidino)-2-morpholino
pyrimidine HCl
13,14,6
2-Amino-5-(4-chlorophenoxy)-4-(3-(hydroxymethyl)piperidino)
pyrimidine 172-173 1,5
2-Amino-5-(4-chlorophenoxy)-4-(2-(2-hydroxyethyl)piperidino)

pyrimidine	153-154	1,4
5-(4-Chlorophenoxy)-4-(2-(2-hydroxyethoxy)ethylamino)-2-morpholinopyrimidine HCl	160-163	13,14,6
2-Anilino-4-(4-hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine	135-136	18,19
2,4-Bis-(4-Hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine HCl	201-202	15
4-(4-Hydroxypiperidino)-5-(phenethyl)pyrimidine HCl	wax	15,12
2-Amino-4-(4-carbamoylpiperidino)-5-(4-chlorophenethyl) pyrimidine	205-206	1,5

Representative Pharmaceutical Compositions

In the following Examples, the "Active Ingredient" may be any compound of Formula I or a pharmaceutically acceptable salt thereof.

Example A - Tablet Composition

	mg/tablet
(a) Active Ingredient	250
(b) Lactose B.P.	210
(c) Povidone B.P.	15
(d) Sodium Starch Glycollate	20
(e) Magnesium Stearate	5

The composition is prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

Example B - Capsule Composition

A capsule composition is prepared by admixing the ingredients and filling into a two-part hard gelatin capsule.

	mg/capsule
(a) Active Ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
(d) Magnesium Stearate	2

Example C - Injectable Composition

(a) Active Ingredient	0.200 g
(b) Hydrochloric Acid Solution 0.1 M or Sodium Hydroxide Solution 0.1M to pH	4.0 to 7.0
(c) Sterile Water q.s. to	10 ml

The active ingredient is dissolved in most of the water (35° - 40° C) and the pH is adjusted to between 4.0 and 7.0. The batch is then made up to volume with sterile water and filtered through a sterile micropore filter into a sterile amber glass vial (type 1) and sealed with sterile closures and overseals.

Neurotrophic Activity

Screen for NGF-like Activity:

Cultured PC12 cells (rat adrenal pheochromocytoma from ATCC) have receptors for NGF. Responses include promotion of neurite outgrowth and elevation of choline acetyltransferase (ChAT) (L.A. Greene and A.S. Tischler, Cell Neurobiol., **3**, 373 (1982)).

The following assay is substantially as described in HL White and PW Scates, Neurochem. Res., **16**, 63 (1991). PC12 cells were cultured at 37° C in DMEM

supplemented with fetal bovine serum, horse serum, glutamine, penicillin, streptomycin and non-essential amino acids. Cultures were split 1:4 every 4 or 5 days. Exponentially dividing cells were plated in fresh medium on collagen-coated 12-well plastic dishes. After allowing one day for cell attachment, the medium was replaced with low serum medium, with or without test compounds and also with or without a limiting concentration of NGF, with each condition in triplicate. The medium may contain up to 0.1% ethanol, which was used as a solvent for most compounds being tested. Cells were examined daily for morphological changes using an Olympus IMT-2 inverted research microscope. After 2 days incubation with test compounds, cells and media were transferred to 1.5 mL Eppendorf tubes. Aliquots of 20 uL were reserved for cell counting and viability determination by trypan blue exclusion. The remaining cell suspensions were centrifuged, and the cell pellets were washed once in serum-free medium and finally resuspended in 30 uL of distilled water containing eserine, an inhibitor of acetylcholinesterase. The suspensions were stored at -80^0 C until they were assayed for choline acetyltransferase. Compounds are judged NGF-like in this primary screen if they (1) increase the activity of choline acetyltransferase, (2) enhance NGF-stimulated neurite outgrowth or (3) potentiate and appear additive with the action of NGF itself.

Choline Acetyltransferase (ChAT) Assays:

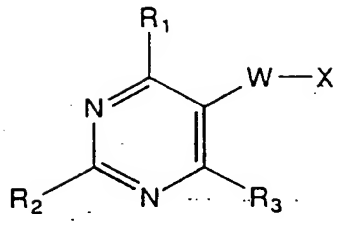
Resuspended cells were lysed by 3 freeze-thaw cycles and 2 x 5 seconds of sonication, using a Heat Systems Ultronic Model W385 with a cup horn attachment. ChAT in cell lysates was determined by the ion exchange procedure of White and Scates (H.L. White and P. W. Scates, Neurochem. Res., **16**, 63 (1991)). The assay involves incubation of cell lysate in a total assay volume of 50 uL containing final concentrations (mM) of potassium phosphate (10), EDTA (0.02), sodium chloride (200), eserine (0.12), choline (0.5), and 0.2 uCi of [^{14}C]acetyl-coenzyme A (0.04). Following a 20 minute incubation at 37^0 C, assay mixtures were applied to 0.5 x 3 cm columns of Bio-Rad AG1-X8 resin (chloride form), and the product, [^{14}C]acetylcholine, was eluted directly into scintillation vials with 1.5 mL of distilled water

In Vitro Activity Data

The compounds according to the invention (1) increased the activity of choline acetyltransferase, (2) enhanced NGF-stimulated neurite outgrowth and/or (3) potentiated or appeared additive with the action of NGF itself. Compounds having especially potent activities: 2-Amino-5-(4-chlorophenoxy)-4-(4-methylpiperazino)pyrimidine; 2-Amino-5-(4-chlorobenzyl)-4-(4-hydroxypiperidino)pyrimidine; 2-Amino-4-[2-(2-hydroxyethyl)ethylamino]-5-(4-chlorobenzyl)pyrimidine; and 2-Amino-5-(4-chlorophenoxy)-4-(4-formylpiperazino)pyrimidine.

CLAIMS

1. A compound of formula I



wherein

W is O, CH2, CH2CH2, OCH2, CH2CH2CH2, or a bond;

R^1 is hydroxyC1-6alkyloxyC1-6alkylamino, diC1-6alkylamino (wherein the alkyl groups may be the same or different), aminoC1-6alkylamino, morpholino, piperidino, piperazino, piperazinoamino, homopiperazino, homopiperidino, homomorpholino, benzoxazino, indolino, 1,2,3,4-tetrahydroquinolino, benzylamino, or anilino wherein C or N atoms may be substituted with one or more substituents selected from the group consisting of:

NR4R5 (wherein R4 and R5 may be the same or different and are H, C1-6alkyl,

hydroxyC1-6alkyl, C3-8cycloalkyl, C6-10aryl, C6-10arylC1-6alkyl, C1-6alkoxy,

C6-10aryloxy or C6-10arylC1-6alkoxy);

NR4R5carbonyC1-6alkyl (wherein R4 and R5 may be the same or different);
OH;
CN;
C1-6alkyl;
C2-7alkenyl;
C2-7alkynyl;
C6-10aryl;
C6-10heteroaryl;
hydroxyC1-6alkyl;
dihydroxyC1-6akyl;
C1-6alkoxy;
C1-6aryloxy;
C6-10heteroaryloxy;
hydroxyC1-6alkoxy;
C1-6alkoxyC1-6alkyl;
C6-10aryloxyC1-6alkyl;
C6-10heteroaryloxyC1-6alkyl;
C3-8cycloalkyl;
C6-10arylC1-6alkyl;
C6-10heteroarylC1-6alkyl;
C6-10arylC1-6alkoxy;
C6-10heteroarylC1-6alkoxy;
C1-6alkylcarbonylC1-6alkyl;
C6-10arylcarbonylC1-6alkyl;
carboxyC1-6alkyl;
C1-6alkoxycarbonylC1-6alkyl;
C6-10aryloxycarbonylC1-6alkyl;
C6-10arylC1-6alkyloxycarbonylC1-6alkyl;
cyanoC1-6alkyl
C1-6alkylthioC1-6alkyl;
C1-6alkylsulfinylC1-6alkyl;
C1-6alkylsulfonylC1-6alkyl;
C6-10arylthioC1-6alkyl;

C6-10arylsulfinylC1-6alkyl;
C6-10arylsulfonylC1-6alkyl;
C6-10arylC1-6alkylthioC1-6alkyl;
C6-10arylC1-6alkylsulfinylC1-6alkyl;
C6-10arylC1-6alkylsulfonylC1-6alkyl;
C6-10heteroarylthioC1-6alkyl;
C6-10heteroarylsulfinylC1-6alkyl;
C6-10heteroarylsulfonylC1-6alkyl;
aziridino;
azetidino;
pyrrolidino;
piperidino;
heptamethyleneimino;
homopiperazino;
N-substituted homopiperazino (wherein the substituent may be C1-6alkyl, C6-10aryl, C6-10arylC1-6alkyl or C6-10heteroaryl);
piperazino;
N-substituted piperazino (wherein the substituent may be C1-6alkyl, C6-10aryl, C6-10 arylC1-6alkyl or C6-10heteroaryl);
morpholino;
homomorpholine;
thiomorpholino;
aminoC1-6alkyl;
C1-6alkylaminoC1-6alkyl;
di(C1-6alkyl)aminoC1-6alkyl (wherein the alkyl groups may be the same or different);
C6-10arylaminoC1-6alkyl;
C6-10arylC1-6alkylaminoC1-6alkyl;
di(C6-10aryl)aminoC1-6alkyl (wherein the aryl groups may be the same or different);

di(C6-10arylC1-6alkyl)aminoC1-6alkyl (wherein the arylalkyl groups may be the same or different);

R12C(O)C1-6alkyl (wherein R12 is aziridino, azetidino, pyrrolidino, piperidino, heptamethyleneimino, piperazino, homopiperazino, morpholino, homomorpholino, or thiomorpholino);

C(O)R6; C(O)C(O)R6; C(S)R6; S(O)2R6; and C(NR11)R6 (wherein R11 is hydrogen, C1-6alkyl or C6-10aryl and R6 may be H or any of the above listed substituents); and

R^2 is selected from the group consisting of:

H;

halogen;

N3;

OR;

SR;

C1-6alkyl;

C6-10aryl;

C6-10arylC1-6alkyl;

C6-10heteroaryl;

NR7R8 (wherein R7 and R8 may be the same or different and are H, C1-6alkyl, hydroxyC1-6alkyl, hydroxyC1-6alkyloxyC1-6alkyl; C3-8cycloalkyl, C6-10aryl, C6-10arylC1-6alkyl, C1-6alkoxy, C6-10aryloxy, C6-10arylC1-6alkoxy, C(O)R6, C(O)C(O)R6, C(S)R6, S(O)2R6, or C(NR11)R6);

N=C(R11)N(R6)2;

aziridino;

azetidino;

pyrrolidino;

piperidino;

hydroxypiperidino;
heptamethyleneimino;
piperazino;
N-substitued piperazino (wherein the substituent may be C1-6alkyl, hydroxyC1-6alkyl, C6-10aryl, C6-10arylC1-6alkyl or C6-10heteroaryl);
homopiperazino;
N-substituted homopiperazino (wherein the substituent may be C1-6alkyl, hydroxyC1-6alkyl, C6-10aryl, C6-10arylC1-6alkyl or C6-10heteroaryl);
morpholino;
homomorpholine;
thiomorpholino; and
R12C(O)C1-6alkyl (wherein R12 is aziridino, azetidino, pyrrolidino, piperidino, heptamethyleneimino, piperizino, homopiperazino, morpholino, homomorpholino, or thiomorpholino);
C-substituted piperidino wherein the substituent is C(O)R6);
C-substituted piperidino (wherein the substituent may be C1-6alkyl, hydroxyC1-6alkyl, C6-10aryl, C6-10arylC1-6alkyl or C6-10heteroaryl);

R^3 is selected from the group consisting of:
H;
OR;
NR9R10 (wherein R9 and R10 may be the same or different and are H, C1-6alkyl, C3-8cycloalkyl, C6-10aryl, or C6-10arylC1-6alkyl);
CF3;
C1-6alkyl;
C6-10aryl;
C6-10arylC1-6alkyl; and
C6-10heteroaryl;

X is a C6-10 aryl ring or a C6-10 heteroaryl ring optionally substituted with one or more suitable substituents for an aryl ring, preferably selected from the group consisting of:

halogen;
C1-6 alkyl;
C2-7alkenyl;
C2-7alkynyl;
C6-10aryl;
C6-10heteroaryl;
OR;
NR9R10 (wherein R9 and R10 may be the same or different and are H, C1-6alkyl,
C3-8cycloalkyl, C6-10aryl, or C6-10arylC1-6alkyl);
NROR;
C(O)NR9R10
C(O)OR;
C(O)R;
NRC(O)NR9R10
NRC(O)R;
NRC(O)OR;
CR(OH)R;
OC(O)R;
S(O)nR wherein R is other than H and n is 0, 1 or 2;
NRS(O)mR wherein R is other than H and m is 1 or 2;
S(O)2NR9R10;
NO2;
CN; and
CF3;
OCF3;

R is H, C1-6alkyl, C3-8cycloalkyl, C6-10aryl or C6-10arylC1-6alkyl; provided that when -W-X is benzyl, R1 is not piperidine; and when R1 is a hydroxyalkyloxyalkylamino, R2 is not a heterocyclic ring;

and pharmaceuticall acceptable esters, amides, salts or solvates thereof.

2. A compound according to claim 1 wherein R1 is attached to the 4-position of the pyrimidine ring, W is O, CH2 or CH2CH2 and X is substituted phenyl.

3. A compound according to claim 1 wherein R1 is attached to the 4-position of the pyrimidine ring, W is O or CH2 and X is substituted phenyl.

4. A compound according to claim 1 wherein R1 is attached to the 4-position of the pyrimidine ring and is 4-(2-hydroxyethyl)piperazino or 2-(2-hydroxyethoxy)ethylamino, W is O or CH2, X is substituted phenyl, and R2 is NH2.

5. A compound according to claim 1 selected from:

2-Amino-4-morpholino-5-(phenoxy)pyrimidine;
2-Amino-5-(4-methylphenoxy)-4-(morpholino)pyrimidine;
2-Amino-5-(4-fluorophenoxy)-4-(morpholino)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine;
2-Amino-5-(4-chlorobenzyloxy)-4-(morpholino)pyrimidine;
2-Amino-5-(benzyloxy)-4-(morpholino)pyrimidine;
2-Amino-5-(4-chlorophenoxymethyl)-4-(morpholino)pyrimidine;
2-Amino-5-(phenoxymethyl)-4-(morpholino)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(2-(2-hydroxyethoxy)ethylamino)pyrimidine;
2-Amino-4-(4-carbamoylpiperidino)-5-(4-chlorophenoxy)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(piperazino)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(4-methylpiperazino)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(4-ethylpiperazino)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;
2-Amino-5-(4-fluorophenoxy)-4-(4-phenylpiperazino)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(4-phenylpiperazino)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(4-(2-pyridyl)piperazino)pyrimidine;
2-Amino-4-(4-benzylpiperazino)-5-(4-chlorophenoxy)pyrimidine;
2-Amino-5-(4-chlorophenyoxy)-4-(4-formylpiperazino)pyrimidine;

4-(4-Acetylpiperazino)-2-amino-5-(4-chlorophenoxy)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-methoxyacetylpiperazino)pyrimidine;

2-Anilino-5-(4-chlorophenoxy)-4-(morpholino)pyrimidine;

5-(4-Chlorophenoxy)-2-(dimethylamino)-4-(4-methylpiperazino)pyrimidine;

5-(4-Chlorophenoxy)-4-morpholino-2-(3-phenylureido)pyrimidine;

5-(4-Chlorophenoxy)-2,4-(dimorpholino)pyrimidine;

5-(4-Chlorophenoxy)-2-(4-methylpiperazino)-4-(morpholino)pyrimidine;

5-(4-Chlorophenoxy)-4-(4-methylpiperazino)-2-(morpholino)pyrimidine;

5-(4-Chlorophenoxy)-4-[4-(2-hydroxyethyl)piperazino]-2-(morpholino)pyrimidine;

2-Amino-5-(4-chloroanilino)-4-(morpholino)pyrimidine;

2-Amino-5-(anilino)-4-(morpholino)pyrimidine;

2-Amino-5-(4-chlorobenzylamino)-4-(morpholino)pyrimidine;

2-Amino-5-(benzylamino)-4-(morpholino)pyrimidine;

2-Amino-5-(4-chloroanilinomethyl)-4-(morpholino)pyrimidine;

2-Amino-5-(anilinomethyl)-4-(morpholino)pyrimidine;

2-Amino-5-benzyl-4-(morpholino)pyrimidine;

2-Amino-5-benzyl-4-(dimethylamino)pyrimidine;

2-Amino-5-(4-methoxybenzyl)-4-(morpholino)pyrimidine;

5-Benzyl-4-[2-(2-hydroxyethoxy)ethylamino]pyrimidine;

2-Amino-5-benzyl-4-(4-hydroxypiperidino)pyrimidine;

2-Amino-5-benzyl-4-(4-methylpiperazinoamino)pyrimidine;

2-Amino-5-benzyl-4-(4-carbamoylpiperidino)pyrimidine;

2-Amino-5-benzyl-4-(4-methylpiperazino)pyrimidine;

2-Amino-5-benzyl-4-(4-hydroxyethylpiperazino)pyrimidine;

5-Benzyl-2,4-bis(4-methylpiperazino)pyrimidine;

5-Benzyl-2,4-(dimorpholino)pyrimidine;

5-Benzyl-2-dimethylamino-4-(4-methylpiperazino)pyrimidine;

2-Amino-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine;

2-Amino-4-(4-ethylpiperazino)-5-(4-methylbenzyl)pyrimidine;

2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-methylbenzyl)pyrimidine;

2-Amino-4-(4-hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine;

2-Amino-5-(4-chlorobenzy)-4-(morpholino)pyrimidine;

2-Amino-4-[2-(2-hydroxyethyl)ethylamino]-5-(4-chlorobenzyl)pyrimidine;
2-Amino-5-(4-chlorobenzyl)-4-(4-methylpiperazino)pyrimidine;
2-Amino-5-(4-chlorobenzyl)-4-(4-ethylpiperazino)pyrimidine;
2-Amino-5-(4-chlorobenzyl)-4-(4-hydroxyethylpiperazino)pyrimidine;
2-Amino-5-(4-chlorobenzyl)-4-(4-hydroxypiperidino)pyrimidine;
2-Amino-5-(4-methoxybenzyl)-4-(4-methylpiperazino)pyrimidine;
2-Amino-5-(4-hydroxybenzyl)-4-(4-methylpiperazino)pyrimidine;
2-Amino-4-(4-methylpiperazino)-5-(isopropylbenzyl)pyrimidine;
2-Amino-4-(4-ethylpiperazino)-5-(4-isopropylbenzyl)pyrimidine;
2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-isopropylbenzyl)pyrimidine;
2-Amino-5-(4-hydroxypiperidino)-4-(4-isopropylbenzyl)pyrimidine;
2-Amino-4-(4-methylpiperazino)-5-(3,4,5-trimethoxybenzyl)pyrimidine;
2-Amino-4-(4-ethylpiperazino)-5-(3,4,5-trimethoxybenzyl)pyrimidine;
2-Amino-4-(4-hydroxyethylpiperazino)-5-(3,4,5-trimethoxybenzyl)pyrimidine;
2-Amino-4-(4-hydroxypiperidino)-5-(3,4,5-trimethoxybenzyl)pyrimidine;
2-Amino-4-(4-methylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)pyrimidine;
2-Amino-4-(4-ethylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)pyrimidine;
2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-[4-chlorobenzyloxy]benzyl)pyrimidine;
2-Amino-4-(4-methylpiperazino)-5-((3-pyridyl)methyl)pyrimidine;
2-Amino-4-(4-ethylpiperazino)-5-[(3-pyridyl)methyl]pyrimidine;
2-Amino-4-(4-hydroxyethylpiperazino)-5-([3-pyridyl]methyl)pyrimidine;
4-Anilino-2-methyl-5-(phenethyl)pyrimidine;
4-Benzylamino-2-methyl-5-(phenethyl)pyrimidine;
4-[2-(2-Hydroxyethoxy)ethylamino]-2-methyl-5-(phenethyl)pyrimidine;
2-Methyl-4-morpholino-5-(phenethyl)pyrimidine;
2,4-Dimorpholino-5-(phenethyl)pyrimidine;
2-Amino-4-morpholino-5-(phenethyl)pyrimidine;
4-Morpholino-5-(phenethyl)pyrimidine;
2-Amino-5-(4-methoxyphenethyl)-4-(morpholino)pyrimidine;
2-Amino-4-morpholino-5-(phenylpropyl)pyrimidine;
2-Amino-4-morpholino-5-(phenyl)pyrimidine;
2-Amino-5-(4-fluorophenyl)-4-(morpholino)pyrimidine;

2-Amino-5-(4-chlorophenyl)-4-(morpholino)pyrimidine;
2-Amino-5-(4-bromophenyl)-4-(morpholino)pyrimidine;
2-Amino-4-(4-chlorophenoxy)-5-(morpholino)pyrimidine;
2-Amino-4-(4-chlorobenzyloxy)-5-(4-methylpiperizino);
2-Amino-4-(4-chlorophenoxy)-5-(4-methylpiperizino)pyrimidine;
4-(4-Chlorophenoxy)-5-(4-methylpiperazino)pyrimidine;
2-Amino-4-(chlorobenzylamino)-5-(4-methylpiperazino);
2-Amino-5-(4-ethylphenoxy)-4-(4-methylpiperazino)pyrimidine;;
2-Amino-5-(2,4-dichlorophenoxy)-4-(4-methylpiperazino)pyrimidine;

2-Amino-5-(4-chloro-2-methylphenoxy)-4-(4-methylpiperazino)pyrimidine ;

2-Amino-5-(3-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(2-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine ;

2-Amino-5-(4-bromophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(4-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;
2-Amino-5-(3-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-trifluoromethylphenoxy)pyrimidine;
2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-methylphenoxy)pyrimidine;

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(3-methylphenoxy)pyrimidine;

2-Amino-4-(4-(2-hydroxyethyl)piperazino-5-(2-methylphenoxy))pyrimidine;

2-Amino-5-(4-ethylphenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-isopropylphenoxy)pyrimidine;

2-Amino-5-(4-butylphenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-methoxyphenoxy)pyrimidine;

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(3-methoxyphenoxy)pyrimidine;

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(2-methoxyphenoxy)pyrimidine;

2-Amino-4-(4-(2-hydroxyethyl)piperazino)-5-(4-(trifluoromethoxy)phenoxy)pyrimidine;

2-Amino-5-(2,4-dichlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(2,3-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(2,4-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(2,6-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(3,5-difluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(4-chloro-2-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(2-chloro-4-fluorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(4-chloro-2-methylphenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-(2-pivaloyloxyethyl)piperazino)pyrimidine;

2-Amino-4-(4-butyrylpiperazino)-5-(4-chlorophenoxy)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-phenoxyacetylpiperazino)pyrimidine;

2-Amino-4-(4-benzoylpiperazino)-5-(4-chlorophenoxy)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-(2-furoyl)piperazino)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-ethoxycarbonylpiperazino)pyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(4-phenoxycarbonylpiperazino)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-methoxydicarbonylpiperazino)pyrimidine;

2-Amino-4-(4-(3-carbamoylpropionyl)piperazino)-5-(4-chlorophenoxy)pyrimidine;
2-Amino-4-(4-(3-carboxypropionyl)piperazino)-5-(4-chlorophenoxy)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-(methlysulfonyl)piperazino)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-(phenylsulfonyl)piperazino)pyrimidine;

5-(4-Chlorophenoxy)-4-(4-methylpiperazino)-2-(1-pyrrolidinyl)pyrimidine;

2-(Anilino)-5-(4-chlorophenoxy)-4-(4-methylpiperazino)pyrimidine;
5-(4-Chlorophenoxy)-2-(4-fluoroanilino)-4-(4-methylpiperazino)pyrimidine;

2-(Benzylamine)-5-(4-chlorophenoxy)-4-(4-methylpiperazino) pyrimidine;

2,4-Bis(4-ethylpiperazino)-5-(4-chlorophenoxy)pyrimidine;
5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(isopropylamino) pyrimidine;
5-(4-Chlorophenoxy)-2-((2-hydroxyethyl)amino)-4-(4-(2-hydroxyethyl)piperazino) pyrimidine;
5-(4-Chlorophenoxy)-2-(2-(2-hydroxyethoxy)ethylamino)-4-(4-(2-hydroxyethyl)piperazino) pyrimidine;
2-(Anilino)-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

5-(4-Chlorophenoxy)-2-(4-fluoroanilino)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(4-methylanilino)pyrimidine;

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(1-pyrrolidinyl)pyrimidine;

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(piperidino)pyrimidine;

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(4-hydroxypiperidino) pyrimidine;

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(4-phenylpiperazino) pyrimidine;

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)-2-(4-methylpiperazino) pyrimidine;

5-(4-Chlorophenoxy)-2-(4-ethylpiperazino)-4-(4-(2-hydroxyethyl)piperazino) pyrimidine;

2,4-Bis(4-(2-hydroxyethyl)piperazino)-5-(4-chlorophenoxy)pyrimidine;

2-Chloro-5-(4-chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

5-(4-Chlorophenoxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

5-(4-Chlorophenoxy)-4-(4-methylpiperazino)pyrimidine;

2-Amino-5-(4-chlorophenyl)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(4-chlorophenyl)-4-(4-methylpiperazino)pyrimidine;

2-Amino-5-(4-fluorobenzyl)-4-(4-methylpiperazino)pyrimidine;

2-Amino-4-(4-hydroxyethylpiperazino)-5-(4-trifluoromethylbenzyl)pyrimidine;

2-(4-Carbamoylpiperidino)-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine;

2-(2-Hydroxyethoxy)ethylamino)-5-(4-methylbenzyl)-4-(4-methylpiperazino)pyrimidine;

2-Amino-5-(4-chlorophenethyl)-4-(4-methylpiperazino)pyrimidine;

2-Amino-5-(4-chlorophenethyl)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(4-chlorobenzyloxy)-4-(4-methylpiperazino)pyrimidine;
2-Amino-5-(4-chlorobenzyloxy)-4-(4-(2-hydroxyethyl)piperazino)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(4-hydroxypiperidino)pyrimidine;
2-Amino-4-(4-hydroxypiperidino)-5-(4-methylphenoxy)pyrimidine;
2-Amino-5-(2,4-dichlorophenoxy)-4-(4-hydroxypiperidino)pyrimidine;
5-(4-Chlorophenoxy)-4-(4-hydroxypiperidino)-2-morpholinopyrimidine;
2-Amino-5-(4-chlorophenoxy)-4-(3-(hydroxymethyl)piperidino)pyrimidine;

2-Amino-5-(4-chlorophenoxy)-4-(2-(2-hydroxyethyl)piperidino)pyrimidine;

5-(4-Chlorophenoxy)-4-(2-(2-hydroxyethoxy)ethylamino)-2-morpholinopyrimidine;
2-Anilino-4-(4-hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine;
2,4-Bis-(4-Hydroxypiperidino)-5-(4-methylbenzyl)pyrimidine;
4-(4-Hydroxypiperidino)-5-(phenethyl)pyrimidine; and
2-Amino-4-(4-carbamoylpiperidino)-5-(4-chlorophenethyl)pyrimidine.

6. A pharmaceutical compositon comprising a compound according to claims 1-5 and a pharmaceutically acceptable carrier therefor.

7. A method of treating a mammal having a neurodegenerative or neurological disorder of the central or peripheral nervous system with a therapeutically effective amount of a compound of formula I according to claim 1, including compounds where -W-X is benzyl and R1 is piperidine, or R1 is a hydroxyalkyloxyalkylamine and R2 is a heterocyclic ring.

8. A method according to claim 7 wherein the disorder is Alzheimer's disease.

9. A method according to claim 7 wherein the disorder is peripheral neuropathy.

10. A method according to claim 7 wherein the disorder is senile dementia.

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(71) Applicant *(for all designated States except US)*: KRENITSKY PHARMACEUTICALS INC. [US/US]; Four University Place, 4611 University Drive, Durham, NC 27707 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KELLEY, James, L. [US/US]; 10928 Raven Rock Drive, Raleigh, NC 27614 (US). KRENITSKY, Thomas, A. [US/US]; 106 Laurel Hill Road, Chapel Hill, NC 27514 (US). BEAUCHAMP, Lilia, M. [US/US]; 3003 Wycliff Road, Raleigh, NC 27607 (US).

(74) Agents: SPRUILL, W., Murray et al.; Bell Seltzer Intellectual Property Law Group, Alston & Bird LLP, P.O. Drawer 34009, Charlotte, NC 28234 (US).

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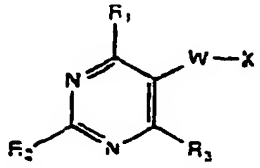
24 June 1999 (24.06.99)

(54) Title: SUBSTITUTED PYRIMIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEURODEGENERATIVE OR NEUROLOGICAL DISORDERS OF THE CENTRAL NERVOUS SYSTEM

(57) Abstract



(I)

The present invention relates to novel derivatives of a series of substituted pyrimidines of formula (I); wherein W is O, CH2, CH2CH2, OCH2, CH2CH2CH2, or a bond; R^1 is hydroxyC1–6alkyloxyC1–6alkylamino, diC1–6alkylamino wherein the alkyl groups may be the same or different, aminoC1–6alkylamino, morpholino, piperidino, piperazino, piperazinoamino, homopiperazino, homopiperidino, homomorpholino, benzoxazino, indolino, 1,2,3,4–tetrahydroquinolino, benzylamino or anilino wherein C or N atoms may be substituted with one or more substituents; R^2 is selected from the group consisting of H; halogen; N3; OR; SR; C1–6alkyl; C6–10aryl; C6–10arylC1–6alkyl; C6–10heteroaryl; NR7R8; N=C(R11)N(R6)2; aziridino; azetidino; pyrrolidino; piperidino; hydroxypiperidino; heptamethyleneimino; piperazino; N–substituted piperazino homopiperazino; N–substituted homopiperazino; morpholino; homomorpholine; thiomorpholino; and R12C(O)C1–6alkyl; C–substituted piperidino; X is a C6–10aryl ring or a C6–10 heteroaryl ring optionally substituted with one or more suitable substituents for an aryl ring; R is H, C1–6alkyl, C3–8cycloalkyl, C6–10aryl or C6–10arylC1–6alkyl; provided that when –W–X is benzyl, R1 is not piperidine; and when R1 is a hydroxyalkyloxyalkylamino, R2 is not a heterocyclic ring; and to pharmaceutical compositions which contain them, to methods for their preparation and to their use in therapy, particularly in the treatment of neurodegenerative or other neurological disorders of the central and peripheral systems.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/48 C07D401/04 C07D239/42 C07D401/12 C07D401/06
C07D239/46 A61K31/505 //C07D239/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HULL R. ET AL.: "70. Synthetic antimalarials. Part III. Some derivatives of mono- and di-alkylpyrimidines" JOURNAL OF THE CHEMICAL SOCIETY,1946, pages 357-362, XP002100113 see third, fourth and fifth compound see page 359; table IV ---	1,6
X	CURD F.H.S. ET AL.: "74. Synthetic antimalarials. Part VII. 2-Arylamino-4-dialkylaminoalkylaminopyrimidines. Variation of substituents in the 5- and the 6-position" JOURNAL OF THE CHEMICAL SOCIETY,1946, pages 378-384, XP002090474 see Ref. No. 4260, page 380, table I see last compound, page 383, table II --- -/--	1,6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
16 April 1999	29. 04. 99

Name and mailing address of the ISA	Authorized officer
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International Application No
PCT/US 98/21517

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HULL R. ET AL.: "9. Synthetic antimalarials. Part XI. The effect of variation of substituents in derivatives of mono- and di-alkylpyrimidines" JOURNAL OF THE CHEMICAL SOCIETY,1947, pages 41-52, XP002090475 see page 42; table I see page 46, line 25 - line 37 ---	1,6
X	GOLDBERG A.: "No. 218. Préparation de quelques 5-benzyl pyrimidines" BULLETIN DE LA SOCIETE CHIMIQUE FRANCE, 1951, pages 895-899, XP002100114 see fifth compound in table on page 897 see second, fifth and last compound in first table on page 898 ---	1,5,6
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X	ROTH B. ET AL.: "5-Benzyl-2,4-diaminopyrimidines as antibacterial agents. I. Synthesis and antibacterial activity in vitro" JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, vol. 5, November 1962, pages 1103-1123, XP002100115 see compound LXXXI see page 1122; table XII ---	1-3,6
X	CHEMICAL ABSTRACTS, vol. 68, no. 3, 15 January 1968 Columbus, Ohio, US; abstract no. 12933y, AROYAN A.A. & KRAMER M.S.: "Synthesis and some reactions of 4-hydroxy-5-(p-alkoxybenzyl)-6-methyl-2-mercapto- (and 2-amino-)pyrimidines" page 1241; column 2; XP002100116 see abstract & ARM. KHIM. ZH., vol. 20, no. 3, 1967, pages 218-225, --- -/--	1-3,5

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/21517

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 71, no. 21, 24 November 1969 Columbus, Ohio, US; abstract no. 101810k, AROYAN A.A. ET AL.: "Pyrimidine derivatives. X. Synthesis of amino and hydrazino derivatives of 2-(methylthio)-5-(p-alkoxybenzyl)-6-methyl pyrimidines, and a study of their antineoplastic activity" page 347; column 1; XP002100117 see abstract & ARM. KHIM. ZH., vol. 22, no. 7, 1969, pages 617-622, ---	1-3,6
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X	CHEMICAL ABSTRACTS, vol. 82, no. 23, 9 June 1975 Columbus, Ohio, US; abstract no. 156209d, AROYAN A.A. ET AL.: "Pyrimidine derivatives. XXXV. Synthesis of 2,4-bis(arylamino)- and 2,4-bis(aryloxy)-5-(p-alkoxybenzyl)-6-methylpyrimidines" page 601; column 1; XP002100119 see formula I see abstract & ARM. KHIM. ZH., vol. 27, no. 12, 1974, pages 1027-1030, ---	1-3,6
X	DE 25 33 710 A (IMPERIAL CHEMICAL INDUSTRIES LTD.) 19 February 1976 see claims 1-6,13,14,25; example 41 --- -/--	1

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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	-/--	

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/21517

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 08 283246 A (NIPPON SODA CO. LTD.) 29 October 1996 see formula I, table 1, compounds 83, 84, 101, 118 and 136 ---	1
A	EP 0 459 819 A (THE WELLCOME FOUNDATION LIMITED) 4 December 1991 see claims 3,4,9-11; examples 13,20,21 ---	1,5,6
A	EP 0 640 599 A (ONO PHARMACEUTICAL CO., LTD.) 1 March 1995 -----	1-6

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INTERNATIONAL SEARCH REPORT

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PCT/US 98/21517

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-10
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [X] Claims Nos.: 1-6 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-6 (all partially)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1-6 (all partially)

An ambiguity arises from the fact that formula (I) in claim 1 differs from the corresponding formula (I) given on page 4 of the description, cf. Article 6 PCT.
However, the preferred sub-groups of formulae (IA), (IB), (IC) and (ID) defined on pages 10/11, and all the examples bear the -W-X moiety in position 5 and the radical R1 in position 4 of the pyrimidine ring. Thus the search covers only compound(-group)s falling under formula (I) in claim 1.

Additionally dependent claim 5 refers to compound(-group)s wherein W denotes -NH- or -NHCH2- which are not covered by formula (I).

The definition of the compounds of formula (I) is too general and/or encompasses too broad a range of different chemical groups, only partly supported by examples in the descriptive part of the application, i.e. claim 1 is considered to be insufficiently substantiated by the description. The vast number of theoretically conceivable compounds resulting from a claim 1 drafted in such an ambiguous way precludes a comprehensive search.
Thus the search was performed on the basis of those claims which are clear and concise and in the light of the examples and reasonable generalisations thereof (cf. claim 5) and includes compounds having therapeutical activities, cf. Articles 6 PCT, 15(4) PCT and Rule 33 PCT, and the PCT International Search Guidelines chapters III-3.6, III-3.7, VIII-2 and X-6.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-6 (all partially)

   Compounds of formula (I) wherein W denotes O, and pharmaceutical compositions containing the same

2. Claims: 1-6 (all partially)

   Compounds of formula (I) wherein W denotes CH_2, and pharmaceutical compositions containing the same

3. Claims: 1,2,5 and 6 (all partially)

   Compounds of formula (I) wherein W denotes CH_2CH_2, and pharmaceutical compositions containing the same

4. Claims: 1,5 and 6 (all partially)

   Compounds of formula (I) wherein W denotes OCH_2, and pharmaceutical compositions containing the same

5. Claims: 1,5 and 6 (all partially)

   Compounds of formula (I) wherein W denotes $CH_2CH_2CH_2$, and pharmaceutical compositions containing the same

6. Claims: 1,5 and 6 (all partially)

   Compounds of formula (I) wherein W denotes a bond, and pharmaceutical compositions containing the same

INTERNATIONAL SEARCH REPORT

Information on patent family members

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